CHNOLOGY DEPARTMENT

Journal of The Chemical Society

PUBLIC
JAN
DETROIT

December 1958

XUM

PUBLICATION COMMITTEE

Chairman

Sir Christopher Ingold, D.Sc., F.R.I.C., F.R.S.

C. C. Addison, D.Sc., Ph.D., F.R.I.C.
Wilson Baker, M.A., D.Sc., F.R.S.
E. Boyland, D.Sc., Ph.D.
I. G. M. Campbell, B.Sc., Ph.D.
N. Campbell, D.Sc., Ph.D.
N. B. Chapman, M.A., Ph.D.
J. Chatt, M.A., Sc.D., F.R.I.C.
P. B. D. de la Mare, D.Sc., Ph.D.
M. J. S. Dewar, M.A., D.Phil.
D. D. Eley, Sc.D., Ph.D.
H. J. Emeléus, C.B.E., M.A., D.Sc., F.R.S.
D. H. Everett, M.B.E., M.A., D.Phil.
G. Gee, Sc.D., A.R.I.C., F.R.S.
T. G. Halsall, Ph.D., M.A., A.R.I.C.
B. A. Hems, D.Sc., F.R.I.C.
D. H. Hey, D.Sc., F.R.I.C., F.R.S.
D. J. G. Ives, D.Sc., A.R.C.S., F.R.I.C.
A. W. Johnson, Sc.D., Ph.D., A.R.C.S.
E. R. H. Jones, D.Sc., F.R.I.C., F.R.S.
G. W. Kenner, M.Sc., Ph.D.
H. C. Longuet-Higgins, M.A., D.Phil., F.R.S.
B. Lythgoe, M.A., Ph.D., F.R.I.C., F.R.S.
A. Neuberger, Ph.D., M.D., F.R.S.
R. G. W. Norrish, Sc.D., F.R.I.C., F.R.S.
H. T. Openshaw, M.A., D.Phil.
M. W. Perrin, C.B.E., M.A., F.R.I.C.
V. Petrow, Ph.D., D.Sc., F.R.I.C.
H. M. Powell, M.A., B.Sc., F.R.S.
P. L. Robinson, D.Sc., F.R.I.C.
K. Schofield, Ph.D., D.Sc., F.R.I.C.
J. C. Speakman, M.Sc., Ph.D., D.Sc.
H. W. Thompson, M.A., D.Sc., F.R.S.
E. E. Turner, M.A., D.Sc., F.R.S.
A. R. J. P. Ubbelohde, M.A., D.Sc., F.R.S.
D. H. Whiffen, M.A., D.Phil.

Editor

R. S. Cahn, M.A., D.Phil.Nat., F.R.I.C.

Assistant Editors

A. D. Mitchell, D.Sc., F.R.I.C.
L. C. Cross, Ph.D., A.R.C.S., F.R.I.C.
A. E. Somerfield, Ph.D.

XUM

XUM

XUM

CONTENTS

General, physical, and inorganic

NO.		PAGE
857	Effect of solvent composition on the kinetics of reactions between ions and dipolar molecules. Part I By E. A. S. Cavell	4217
858	Metallic complexes of dimethyl-*o*-methylthiophenylarsine. Part I. Complexes of nickel and palladium By Stanley E. Livingstone	4222
862	Complexes of titanium and zirconium halides with organic ligands By H. J. Emeléus and G. S. Rao	4245
865	Investigations on the co-ordinative power of uranyl. Part III. Infrared spectra of some complexes with β-diketones By L. Sacconi, G. Caroti, and P. Paoletti	4257
869	2 : 2′-Dipyridyl complexes of cobalt, rhodium, and iridium. Part I. Tervalent rhodium and iridium complexes By B. Martin and Gwyneth M. Waind	4284
870	The catalytic hydrogenation of unsaturated hydrocarbons. Part II. Reaction between dideuteroacetylene and hydrogen over a nickel–pumice catalyst By G. C. Bond	4288
876	π-*cyclo*Pentadienylrhenium carbonyl compounds By M. L. H. Green and G. Wilkinson	4314
881	Infrared spectra, structure, and hydrogen-bonding in ammonium salts By T. C. Waddington	4340
886	Reactions of tin(IV) halides with ammonia derivatives. Part II. The reaction of liquid ammonia with tin(IV) bromide, diammonium hexabromostannate(IV), and tin(IV) iodide By E. Bannister and G. W. A. Fowles	4374
890	Higher complex fluorides of molybdenum By G. B. Hargreaves and R. D. Peacock	4390
898	The relationship between the excess heat and volume of mixing By A. R. Mathieson	4444
915	Infrared spectra and hydrogen bonding in the nickel–dimethylglyoxime and related complexes By R. Blinc and D. Hadži	4536
919	Transition-metal complexes of seven-membered ring systems. Part I. The *cyclo*-heptatriene–metal complexes and related compounds By E. W. Abel, M. A. Bennett, R. Burton, and G. Wilkinson	4559
933	Electron spin resonance spectra of the carboxyhydroxymethyl radical trapped after γ-irradiation of glycollic acid By P. M. Grant, R. B. Ward, and D. H. Whiffen	4635
935	The conductances of some chlorides in ethanol. Part II. Electrolytic behaviour of zirconium chloride ethoxides By A. M. El-Aggan, D. C. Bradley, and W. Wardlaw	4643
936	Some chloride alkoxides of quadrivalent vanadium and quinquevalent molybdenum By D. C. Bradley, R. K. Multani, and W. Wardlaw	4647
937	Chloroalkoxides of titanium, zirconium, cerium, and thorium By D. C. Bradley, R. N. P. Sinha, and W. Wardlaw	4651
938	The chemistry of uranyl acetylacetone complex By Alan E. Comyns, Bryan M. Gatehouse, and Eric Wait	4655
943	Reactions of disodium pentacyanoamminoferrate with aromatic amines. Part II. The preparation and properties of compounds containing the pentacyano-(*p*-anilinoanilino)ferrate ion By E. F. G. Herington	4683

XUM

NO. PAGE

949 Condensed ions in aqueous solution. Part I. Ion-exchange behaviour of vanadate ions
By R. U. RUSSELL and J. E. SALMON 4708

955 The catalytic hydrogenation of unsaturated hydrocarbons. Part III. The kinetics of the hydrogenation of acetylene over various types of nickel catalyst
By G. C. BOND and R. S. MANN 4738

NOTES

965 Reactions of disodium pentacyanoamminoferrate with aromatic amines. Part III. The preparation of 2 : 7-dimethylphenazine from *p*-toluidine
By E. F. G. HERINGTON 4771

972 Thallous *tert.*-amyloxide
By D. C. BRADLEY 4780

975 Thallous borohydride, $TlBH_4$
By T. C. WADDINGTON 4783

Physical organic

866 A further study of the thermal decomposition of 3 : 5-dibromobenzene 1 : 4-diazo-oxide
By M. J. S. DEWAR and A. N. JAMES 4265

877 Intermediates in allylic rearrangements. Part I. The anionotropy of 1- and 3-phenylallyl *p*-nitrobenzoate
By Y. POCKER 4318

878 Intermediates in allylic rearrangements. Part II. Rates and mechanism of exchange and rearrangement in 1- and 3-phenylallyl benzoate
By Y. POCKER 4323

879 Reactivities of aromatic hydrocarbons. Part I. Bromination
By S. F. MASON 4329

883 The rearrangement of aromatic *N*-nitroamines. Part II. Isotopic test for intramolecular character in the nitro-transfers from side-chain to *ortho*- and *para*-positions
By S. BROWNSTEIN, C. A. BUNTON, and E. D. HUGHES 4354

884 Nitration at nitrogen and oxygen centres. Part I. Kinetics and mechanism of the conversion of secondary amines into nitroamines
By E. D. HUGHES, SIR CHRISTOPHER INGOLD, and R. B. PEARSON 4357

885 Nitration at nitrogen and oxygen centres. Part II. Kinetics and mechanism of the conversion of alcohols, glycols, and glycerol into their nitric esters
By EILEEN L. BLACKALL, E. D. HUGHES, SIR CHRISTOPHER INGOLD, and R. B. PEARSON 4366

887 Relation between hyperconjugation and conformation. Part III. Ethyl alcoholysis of some derivatives of diphenylmethyl chloride
By G. BADDELEY and M. GORDON 4379

888 The electric dipole moments of a vinylenic series
By M. HELY HUTCHINSON and L. E. SUTTON 4382

889 Kinetics of the acid and alkaline hydrolysis of potassium ethoxycarbonylmethanesulphonate
By R. P. BELL and D. J. RAWLINSON 4387

893 Homolytic aromatic substitution. Part XVI. Relative rates of *p*-bromophenylation of nitrobenzene and *p*-nitrophenylation of bromobenzene. Derivation and discussion of partial rate factors
By CHANG SHIH, D. H. HEY, and GARETH H. WILLIAMS 4403

920 The activation of carbon–carbon double bonds by cationic catalysts. Part VI. Effect of substituents on the dimerisation of 1 : 1-diarylethylenes catalysed by trichloroacetic acid
By ALWYN G. EVANS, PETER M. S. JONES, and J. H. THOMAS 4563

934 Organic peroxides. Part IX. A stereochemical study of the formation of alkyl hydroperoxides from hydrogen peroxide
By ALWYN G. DAVIES and R. FELD 4637

XUM

NO. PAGE

940 The chemical effects of γ-radiation on organic systems. Part I. The systems pyridine–bromobenzene and aniline–bromobenzene
By G. A. SWAN and P. S. TIMMONS 4669

941 The chemical effects of γ-radiation on organic systems. Part II. The action of radiation on benzyl alcohol alone or mixed with acetone or bromobenzene
By G. A. SWAN and D. WRIGHT 4673

942 Infrared spectra and the polymorphism of glycerides. Part V. 1 : 2-Diglycerides
By D. CHAPMAN 4680

957 Tracer studies on alcohols. Part IV. The oxygen exchange and racemisation of 4-methoxydiphenylmethanol
By C. A. BUNTON, D. R. LLEWELLYN, and I. WILSON 4747

958 Nucleophilic displacements in organic sulphites. Part I. The positions of bond fission in the hydrolyses of some 1 : 2- and 1 : 3-cyclic sulphites
By C. A. BUNTON, P. B. D. DE LA MARE, (MISS) P. M. GREASELEY, D. R. LLEWELLYN, N. H. PRATT, and J. G. TILLETT 4751

959 Nucleophilic displacements in organic sulphites. Part II. The acid-catalysed hydrolysis of ethylene sulphite and of trimethylene sulphite
By C. A. BUNTON, P. B. D. DE LA MARE, and J. G. TILLETT 4754

960 Nucleophilic displacements in organic sulphites. Part III. Comparison of alkaline and acidic hydrolyses of trimethylene sulphite and related compounds
By C. A. BUNTON, P. B. D. DE LA MARE, (MISS) A. LENNARD, D. R. LLEWELLYN, R. B. PEARSON, J. G. PRITCHARD, and J. G. TILLETT 4761

NOTES

961 Nucleophilic displacements in organic sulphites. Part IV. The effects of added salts on the solubility of ethylene sulphite
By E. D. DAVIES and J. G. TILLETT 4766

962 A rapid method for the calculation of the molecular-orbital secular equation
By D. S. URCH 4767

Organic

859 Xanthones: cyclisation of 3′-substituted 2-carboxydiphenyl ethers
By A. A. GOLDBERG and A. H. WRAGG 4227

860 Reactivity of xanthones bearing 1- and 3-chloro-substituents towards nucleophilic reagents
By A. A. GOLDBERG and A. H. WRAGG 4234

861 Deoxynucleosides and related compounds. Part VIII. Some further transformations of O^2 : 2′-*cyclo*uridine
By D. M. BROWN, D. B. PARIHAR, and SIR ALEXANDER TODD 4242

863 Bis-*o*-phenylene pyrophosphite: a new reagent for peptide synthesis. Part I. The preparation of some *o*-phenylene pyrophosphites
By P. C. CROFTS, J. H. H. MARKES, and H. N. RYDON 4250

864 The synthesis of tri- and tetra-alkylpyrroles
By A. W. JOHNSON, E. MARKHAM, R. PRICE, and K. B. SHAW 4254

867 Strength of chloro-substituted phenoxyacetic and related phosphorus-containing acids
By J. N. PHILLIPS 4271

868 Synthetical studies relating to colchicine. Part I. Some derivatives of 1 : 2-benzo*cyclo*hept-1-en-4-one
By T. A. CRABB and K. SCHOFIELD 4276

871 Studies in polycyclic systems. Part IV. Synthesis of some degradation products of dextropimaric acid and related diterpenoids
By D. NASIPURI and A. C. CHAUDHURI 4299

872 Polymerisation of flavans. Part II. The condensation of 4′-methoxyflavan with phenols
By B. R. BROWN and W. CUMMINGS 4302

873 The synthesis of benzofurans
By B. R. BROWN, G. A. SOMERFIELD, and P. D. J. WEITZMAN 4305

XUM

NO.		PAGE
874	Carcinogenic nitrogen compounds. Part XXVI. Nitrogen-heterocyclic compounds derived from some polycyclic arylamines By Ng. Ph. Buu-Hoï, G. Saint-Ruf, P. Jacquignon, and G. C. Barrett	4308
875	Phthalans. Part II. Ultraviolet and infrared spectra By W. R. Allison, W. R. Logan, G. T. Newbold, and T. J. Ross	4311
880	Pavine. Part III. Related synthetic work By A. R. Battersby and R. Binks	4333
882	Isolation and structure of ribitol phosphate derivatives (teichoic acids) from bacterial cell walls By J. J. Armstrong, J. Baddiley, J. G. Buchanan, B. Carss, and G. R. Greenberg	4344
891	The constitution and synthesis of anisoxide By D. H. R. Barton, A. Bhati, P. de Mayo, and G. A. Morrison	4393
892	The generalised diaxial ⟶ diequatorial rearrangement By D. H. R. Barton and J. F. King	4398
894	Gum ghatti (Indian gum). Part III. Neutral oligosaccharides formed on partial acid hydrolysis of the gum By G. O. Aspinall, (Mrs.) Barbara J. Auret, and E. L. Hirst	4408
895	Immunopolysaccharides. Part XI. Structure of an *Acetobacter capsulatum* dextran By S. A. Barker, E. J. Bourne, G. T. Bruce, and M. Stacey	4414
896	The reaction between 3-chloro-3-methylbutyne and methyl sodioacetoacetate By L. Crombie and K. Mackenzie	4417
897	Lipids. Part VII. Synthesis of 8-hydroxyoctadec-*cis*-11- and -*trans*-11-en-9-ynoic acid: the status of natural 8-hydroxyximenynic acid By L. Crombie and B. P. Griffin	4435
899	Substituted benzidines and related compounds as reagents in analytical chemistry. Part XV. Some new 3 : 3′-disubstituted naphthidines By R. Belcher, S. J. Lyle, and W. I. Stephen	4454
900	Pharmacodynamic compounds. Part I. Some antispasmodics derived from substituted 2-pyrrolidinylalkanols By F. P. Doyle, M. D. Mehta, G. S. Sach, and (in part) J. L. Pearson	4458
901	The structure of viridogrisein (etamycin) By R. B. Arnold, A. W. Johnson, and A. B. Mauger	4466
902	Some stereochemical studies of lignans By A. J. Birch, Barton Milligan, (Mrs.) E. Smith, and R. N. Speake	4471
903	The biosynthesis of polysaccharides. Part I. The composition of plum-leaf polysaccharides By P. Andrews and L. Hough	4476
904	The biosynthesis of polysaccharides. Part II. Incorporation of $^{14}CO_2$ into plum-leaf polysaccharides during photosynthesis By P. Andrews and L. Hough	4483
905	3 : 5-*cyclo*Ergosta-7 : 22-dien-6β-ol and 3 : 5-*cyclo*ergosta-7 : 9(11) : 22-trien-6β-ol By G. H. R. Summers	4489
906	The synthesis of 1 : 9-9′ : 1′-dicarbazolylene, and related experiments By A. E. Jean Herbert and Muriel Tomlinson	4492
907	The oxidation of derivatives of *o*-phenylenediamine. Part VI. Reductive acylation of anilino*apo*safranines and related compounds By Vincent C. Barry, J. G. Belton, J. F. O'Sullivan, and Dermot Twomey	4495
908	Organic peroxides. Part II. The decomposition of bisdiphenylmethyl peroxide By J. I. G. Cadogan, D. H. Hey, and W. A. Sanderson	4498
909	Alkaline degradation of polysaccharides. Part V. Periodate oxycellulose By D. O'Meara and G. N. Richards	4504
910	Studies in pyrolysis. Part XIII. Competitive alkyl–oxygen and acyl–oxygen scission in the pyrolysis of esters; αα-disubstituted cyanomethyl carboxylates By R. N. Bennett, A. A. Deans, J. G. H. Harris, P. D. Ritchie, and J. S. Shim	4508

XUM

NO.		PAGE
911	Studies in pyrolysis. Part XIV. The pyrolysis of 2 : 2-dimethyltrimethylene dibenzoate By A. Golomb and P. D. Ritchie	4515
912	Sesquiterpenoids. Part XI. The constitution of geigerin By D. H. R. Barton and J. E. D. Levisalles	4518
913	Thiol-esters. Part II. The chlorination of 2-diethylaminoethyl thiolbenzoate and the rearrangement of 2-alkylaminoethyl thiolbenzoates By C. J. M. Stirling	4524
914	Intramolecular aminolysis of amides By C. J. M. Stirling	4531
916	Some synthetic cysteinyl peptides By H. S. Bachelard and V. M. Trikojus	4541
917	Urinary steroids and related compounds. Part II. 11 : 17-Disubstituted androstanes carrying no substituent at position 3 By W. Klyne and Sheila Palmer (*née* Ridley)	4545
918	Spirans. Part II. The preparation and ozonolysis of derivatives of 3-ethylidenegris-2′-ene. Anomalous enolisation in β-oxo-esters By F. M. Dean, Thomas Francis, and Kamchorn Manunapichu	4551
921	The oxidation of phenolic ethers with peroxyacetic acid By H. Davidge, Alwyn G. Davies, J. Kenyon, and R. F. Mason	4569
922	The *Senecio* alkaloids. Part XIII. The absolute configuration of heliotridane (1-methylpyrrolizidine) and the "necine" bases By F. L. Warren and M. E. von Klemperer	4574
923	Studies in relation to biosynthesis. Part XVII. Sclerotiorin, citrinin, and citromycetin By A. J. Birch, P. Fitton, E. Pride, A. J. Ryan, Herchel Smith, and W. B. Whalley	4576
924	Studies in relaticn to biosynthesis. Part XVIII. Penicillic acid By A. J. Birch, G. E. Blance, and Herchel Smith	4582
925	Thiazolidines. Part I. Some reactions of 4-benzylidene-2-thiothiazolid-5-one with glycine derivatives By D. O. Holland and P. Mamalis	4584
926	Thiazolidines. Part II. Some reactions of 5-phenyl-2-thiothiazolidine-4-carboxylic acid By D. O. Holland and P. Mamalis	4588
927	Thiazolidines. Part III. The reaction of 2-methylthio-5-phenylthiazoline-4-carboxylic acid with thionyl chloride and phosphorus pentachloride By D. O. Holland and P. Mamalis	4596
928	Thiazolidines. Part IV. Further reactions of 2-methylthio-5-phenylthiazoline-4-carboxylic acid By D. O. Holland and P. Mamalis	4601
929	Thiazolidines. Part V. Synthesis of β-alkylcysteines By F. P. Doyle, D. O. Holland, P. Mamalis, and A. Norman	4605
930	Use of 20-oximes and 20-semicarbazones in making cortisol and 4 : 5α-dihydrocortisol By S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and L. J. Wyman	4614
931	Naphtho(2′ : 3′-2 : 3)furan-4-one By P. Emmott and R. Livingstone	4629
932	Properties and reactions of free alkyl radicals in solution. Part XII. Evidence for radical-catalysis of hydrogen transfer By R. A. Jackson and William A. Waters	4632
939	Interdependence of conformation and conjugation in aromatic ethers. Part III By G. Baddeley and M. A. Vickars	4665
944	Hydroaromatic steroid hormones. Part VI. Some D-homo-analogues lacking ring B By A. J. Birch, E. Pride, and Herchel Smith	4688

XUM

NO.		PAGE
945	The conversion of certain αz-disubstituted *N*-phenylglycines into 4-oxo-1-phenyl-Δ^2-pyrrolines By R. J. S. Beer, W. T. Gradwell, and (in part) W. J. Oates	4693
946	The alkaloids of the Amaryllidaceae. Part III. Hæmanthamine (natalensine) By F. L. Warren and Winifred G. Wright	4696
947	The alkaloids of the Amaryllidaceae. Part IV. The alkaloids of *Brunsvigia cooperi* Baker By L. J. Dry, (Miss) M. Poynton, M. E. Thompson, and F. L. Warren	4701
948	The reaction of 3-bromo-4-iodotoluene with magnesium and lithium By Roy C. Hinton, Frederick G. Mann, and Ian T. Millar	4704
950	The relation between dextro- and *iso*dextro-pimaric acid By B. Green, Adelaide Harris, and W. B. Whalley	4715
951	1 : 7 : 10- and 1 : 6 : 10-Trimethylphenanthrene By J. A. Corran and W. B. Whalley	4719
952	Synthesis of plant-growth regulators. Part V. (3-Substituted 2-naphthyloxy)-*n*-alkanecarboxylic acids By D. Woodcock and B. L. Davies	4723
953	Furan and tetrahydrofuran compounds analogous to ganglion-blocking agents of the 3-oxapentane-1 : 5-bistrialkylammonium series By E. W. Gill and H. R. Ing.	4728
954	The preparation of (±)-α- and (±)-β-grisan-3 : 4′-diol and the resolution of the α-isomer By P. McCloskey	4732
956	The synthesis and properties of 2-azafluoranthene By Neil Campbell and Kenneth F. Reid	4743

Notes

963	Characterisation of thiols by means of their *p*-*p*′-nitrophenylazobenzoyl derivatives By El S. Amin	4769
964	Preparation of ethyl 1-methyl-2 : 4-dioxo*cyclo*hexane-1-carboxylate By S. M. Mukherji, R. K. Sharma, and O. P. Vig	4770
966	Studies in relation to biosynthesis. Part XIX. The biosynthesis of helminthosporin By A. J. Birch, A. J. Ryan, and Herchel Smith	4773
967	Hydroaromatic steroid hormones. Part VII. (±)-17*a*-Ethynyl-17*a*-hydroxy-D-homo-18 : 19-bisnorandrost-4-en-3-one. By A. J. Birch, G. A. Hughes, and Herchel Smith	4774
968	The indole alkaloids. Part II. Vobtusine and voacangine from *Voacanga dregei* By B. O. G. Schuler, A. A. Verbeek, and F. L. Warren	4776
969	The reaction of ethyl diazoacetate with thionaphthen By G. M. Badger, H. J. Rodda, and Jenneth M. Sasse	4777
970	1-Ethyl-3-methyl*cyclo*pentadiene By D. A. H. Taylor	4779
971	Michael addition of 1-methyloxindole and dimethyl acetylenedicarboxylate By J. A. Ballantine, R. J. S. Beer, and Alexander Robertson	4779
973	Bromination of *N*-phenylsydnone By F. Stansfield	4781
974	Oxidative dimerisation of oxindoles By John Harley-Mason and R. F. J. Ingleby.	4782
976	Hydrolysis of ethyl 3-oxo-octadecanoate By D. W. S. Evans	4784

INDEX OF AUTHORS' NAMES

Abel, E. W., Bennett, M. A., Burton, R., and Wilkinson, G., **4559**
Allison, W. R., Logan, W. R., Newbold, G. T., and Ross, T. J., **4311**
Amin, El S., **4769**
Andrews, P., and Hough, L., **4476**, **4483**
Armstrong, J. J., Baddiley, J., Buchanan, J. G., Carss, B., and Greenberg, G. R., **4344**
Arnold, R. B., Johnson, A. W., and Mauger, A. B., **4466**
Aspinall, G. O., Auret, B. J., and Hirst, E. L., **4408**
Auret, B. J. See Aspinall, G. O., **4408**
Bachelard, H. S., and Trikojus, V. M., **4541**
Baddeley, G., and Gordon, M., **4379**
Baddeley, G., and Vickars, M. A., **4665**
Baddiley, J. See Armstrong, J. J., **4344**
Badger, G. M., Rodda, H. J., and Sasse, J. M., **4777**
Ballantine, J. A., Beer, R. J. S., and Robertson, A., **4779**
Bannister, E., and Fowles, G. W. A., **4374**
Barker, S. A., Bourne, E. J., Bruce, G. T., and Stacey, M., **4414**
Barrett, G. C. See Buu-Hoï, Ng. Ph., **4308**
Barry, V. C., Belton, J. G., O'Sullivan, J. F., and Twomey, D., **4495**
Barton, D. H. R., Bhati, A., de Mayo, P., and Morrison, G. A., **4393**
Barton, D. H. R., and King, J. F., **4398**
Barton, D. H. R., and Levisalles, J. E. D., **4518**
Battersby, A. R., and Binks, R., **4333**
Beer, R. J. S., Gradwell, W. T., and Oates, W. J., **4693**
Beer, R. J. S. See also Ballantine, J. A., **4779**
Belcher, R., Lyle, S. J., and Stephen, W. I., **4454**
Bell, R. P., and Rawlinson, D. J., **4387**
Belton, J. G. See Barry, V. C., **4495**
Bennett, M. A. See Abel, E. W., **4559**
Bennett, R. N., Deans, A. A., Harris, J. G. H., Ritchie, P. D., and Shim, J. S., **4508**
Bhati, A. See Barton, D. H. R., **4393**
Binks, R. See Battersly, A. R., **4333**
Birch, A. J., Blance, G. E., and Smith, H., **4582**
Birch, A. J., Fitton, P., Pride, E., Ryan, A. J., Smith, H., and Whalley, W. B., **4576**
Birch, A. J., Hughes, G. A., and Smith, H., **4774**
Birch, A. J., Milligan, B., Smith, E., and Speake, R. N., **4471**
Birch, A. J., Pride, E., and Smith, H., **4688**
Birch, A. J., Ryan, A. J., and Smith, H., **4773**
Blackall, E. L., Hughes, E. D., Ingold, Sir C., and Pearson, R. B., **4366**
Blance, G. E. See Birch, A. J., **4582**
Blinc, R., and Hadži, D., **4536**
Bond, G. C., **4288**
Bond, G. C., and Mann, R. S., **4738**
Bourne, E. J. See Barker, S. A., **4414**
Bradley, D. C., **4780**
Bradley, D. C., Multani, R. K., and Wardlaw, W., **4647**
Bradley, D. C., Sinha, R. N. P., and Wardlaw, W., **4651**
Bradley, D. C. See also El-Aggan, A. M., **4643**
Brooks, S. G., Evans, R. M., Green, G. F. H., Hunt, J. S., Long, A. G., Mooney, B., and Wyman, L. J., **4614**
Brown, B. R., and Cummings, W., **4302**
Brown, B. R., Somerfield, G. A., and Weitzman, P. D. J., **4305**
Brown, D. M., Parihar, D. B., and Todd, Sir A., **4242**
Brownstein, S., Bunton, C. A., and Hughes, E. D., **4354**
Bruce, G. T. See Barker, S. A., **4414**
Buchanan, J. G. See Armstrong, J. J., **4344**
Bunton, C. A., de la Mare, P. B. D., Greaseley, P. M., Llewellyn, D. R., Pratt, N. H., and Tillett, J. G., **4751**
Bunton, C. A., de la Mare, P. B. D., Lennard, A., Llewellyn, D. R., Pearson, R. B., Pritchard, J. G., and Tillett, J. G., **4761**
Bunton, C. A., de la Mare, P. B. D., and Tillett, J. G., **4754**
Bunton, C. A., Llewellyn, D. R., and Wilson, I., **4747**
Bunton, C. A. See also Brownstein, S., **4354**
Burton, R. See Abel, E. W., **4559**
Buu-Hoï, Ng. Ph., Saint-Ruf, G., Jacquignon, P., and Barrett, G. C., **4308**
Cadogan, J. I. G., Hey, D. H., and Sanderson, W. A., **4498**
Campbell, N., and Reid, K. F., **4743**
Caroti, G. See Sacconi, L., **4257**
Carss, B. See Armstrong, J. J., **4344**
Cavell, E. A. S., **4217**
Chang Shih, Hey, D. H., and Williams, G. H., **4403**
Chapman, D., **4680**
Chaudhuri, A. C. See Nasipuri, D., **4299**
Comyns, A. E., Gatehouse, B. M., and Wait, E., **4655**
Corran, J. A., and Whalley, W. B., **4719**
Crabb, T. A., and Schofield, K., **4276**
Crofts, P. C., Markes, J. H. H., and Rydon, H. N., **4250**
Crombie, L., and Griffin, B. P., **4435**
Crombie, L., and Mackenzie, K., **4417**
Cummings, W. See Brown, B. R., **4302**
Davidge, H., Davies, Alwyn G., Kenyon, J., and Mason, R. F., **4569**
Davies, Alwyn G., and Feld, R., **4637**
Davies, Alwyn G. See also Davidge, H., **4569**
Davies, B. L. See Woodcock, D., **4723**
Davies, E. D., and Tillett, J. G., **4766**
Dean, F. M., Francis, T., and Manunapichu, K., **4551**
Deans, A. A. See Bennett, R. N., **4508**
de la Mare, P. B. D. See Bunton, C. A., **4751**, **4754**, **4761**
de Mayo, P. See Barton, D. H. R., **4393**
Dewar, M. J. S., and James, A. N., **4265**
Doyle, F. P., Holland, D. O., Mamalis, P., and Norman, A., **4605**
Doyle, F. P., Mehta, M. D., Sach, G. S., and Pearson, J. L., **4458**
Dry, L. J., Poynton, M., Thompson, M. E., and Warren, F. L., **4701**
El-Aggan, A. M., Bradley, D. C., and Wardlaw, W., **4643**
Emeléus, H. J., and Rao, G. S., **4245**
Emmott, P., and Livingstone, R., **4629**
Evans, A. G., Jones, P. M. S., and Thomas, J. H., **4563**
Evans, D. W. S., **4784**
Evans, R. M. See Brooks, S. G., **4614**

Feld, R. See Davies, Alwyn G., 4637
Fitton, P. See Birch, A. J., 4576
Fowles, G. W. A. See Bannister, E., 4374
Francis, T. See Dean, F. M., 4551
Gatehouse, B. M. See Comyns, A. E., 4655
Gill, E. W., and Ing, H. R., 4728
Goldberg, A. A., and Wragg, A. H., 4227, 4234
Golomb, A., and Ritchie, P. D., 4515
Gordon, M. See Baddeley, G., 4379
Gradwell, W. T. See Beer, R. J. S., 4693
Grant, P. M., Ward, R. B., and Whiffen, D. H., 4635
Greaseley, P. M. See Bunton, C. A., 4751
Green, B., Harris, A., and Whalley, W. B., 4715
Green, G. F. H. See Brooks, S. G., 4614
Green, M. L. H., and Wilkinson, G., 4314
Greenberg, G. R. See Armstrong, J. J., 4344.
Griffin, B. P. See Crombie, L., 4435
Hadži, D. See Blinc, R., 4536
Hargreaves, G. B., and Peacock, R. D., 4390
Harley-Mason, J., and Ingleby, R. F. J., 4782
Harris, A. See Green, B., 4715
Harris, J. G. H. See Bennett, R. N., 4508
Herbert, A. E. J., and Tomlinson, M., 4492
Herington, E. F. G., 4683, 4771
Hey, D. H. See Cadogan, J. I. G., 4498, and Chang Shih, 4403
Hinton, R. C., Mann, F. G., and Millar, I. T., 4704
Hirst, E. L. See Aspinall, G. O., 4408
Holland, D. O., and Mamalis, P., 4584, 4588, 4596, 4601
Holland, D. O. See also Doyle, F. P., 4605
Hough, L. See Andrews, P., 4476, 4483
Hughes, E. D., Ingold, Sir C., and Pearson, R. B., 4357
Hughes, E. D. See also Blackall, E. L., 4366, and Brownstein, S., 4354
Hughes, G. A. See Birch, A. J., 4774
Hunt, J. S. See Brooks, S. G., 4614
Hutchinson, M. H., and Sutton, L. E., 4382
Ing, H. R. See Gill, E. W., 4728
Ingleby, R. F. J. See Harley-Mason, J., 4782
Ingold, Sir C. See Blackall, E. L., 4366, and Hughes, E. D., 4357
Jackson, R. A., and Waters, W. A., 4632
Jacquignon, P. See Buu-Hoï, Ng. Ph., 4308
James, A. N. See Dewar, M. J. S., 4265
Johnson, A. W., Markham, E., Price, R., and Shaw, K. B., 4254
Johnson, A. W. See also Arnold, R. B., 4466
Jones, P. M. S. See Evans, A. G., 4563
Kenyon, J. See Davidge, H., 4569
King, J. F. See Barton, D. H. R., 4398
Klyne, W., and Palmer, S., 4545
Lennard, A. See Bunton, C. A., 4761
Levisalles, J. E. D. See Barton, D. H. R., 4518
Livingstone, R. See Emmott, P., 4629
Livingstone, S. E., 4222
Llewellyn, D. R. See Bunton, C. A., 4747, 4751, 4761
Logan, W. R. See Allison, W. R., 4311
Long, A. G. See Brooks, S. G., 4614
Lyle, S. J. See Belcher, R., 4454
McCloskey, P., 4732
Mackenzie, K. See Crombie, L., 4417
Mamalis, P. See Doyle, F. P., 4605, and Holland, D. O., 4584, 4588, 4596, 4601
Mann, F. G. See Hinton, R. C., 4704
Mann, R. S. See Bond, G. C., 4738
Manunapichu, K. See Dean, F. M., 4551
Markes, J. H. H. See Crofts, P. C., 4250
Markham, E. See Johnson, A. W., 4254
Martin, B., and Waind, G. M., 4284
Mason, R. F. See Davidge, H., 4569
Mason, S. F., 4329
Mathieson, A. R., 4444
Mauger, A. B. See Arnold, R. B., 4466
Mehta, M. D. See Doyle, F. P., 4458
Millar, I. T. See Hinton, R. C., 4704
Milligan, B. See Birch, A. J., 4471
Mooney, B. See Brooks, S. G., 4614
Morrison, G. A. See Barton, D. H. R., 4393
Multani, R. K. See Bradley, D. C., 4647
Mukherji, S. M., Sharma, R. K., and Vig, O. P., 4770
Nasipuri, D., and Chaudhuri, A. C., 4299
Newbold, G. T. See Allison, W. R., 4311
Norman, A. See Doyle, F. P., 4605
Oates, W. J. See Beer, R. J. S., 4693
O'Meara, D., and Richards, G. N., 4504
O'Sullivan, J. F. See Barry, V. C., 4495
Palmer, S. See Klyne, W., 4545
Paoletti, P. See Sacconi, L., 4257
Parihar, D. B. See Brown, D. M., 4242
Peacock, R. D. See Hargreaves, G. B., 4390
Pearson, J. L. See Doyle, F. P., 4458
Pearson, R. B. See Blackall, E. L., 4366, Bunton, C. A., 4761, and Hughes, E. D., 4357
Phillips, J. N., 4271
Pocker, Y., 4318, 4323
Poynton, M. See Dry, L. J., 4701
Pratt, N. H. See Bunton, C. A., 4751
Price, R. See Johnson, A. W., 4254
Pride, E. See Birch, A. J., 4576, 4688
Pritchard, J. G. See Bunton, C. A., 4761
Rao, G. S. See Emeléus, H. J., 4245
Rawlinson, D. J. See Bell, R. P., 4387
Reid, K. F. See Campbell, N., 4743
Richards, G. N. See O'Meara, D., 4504
Ritchie, P. D. See Bennett, R. N., 4508, and Golomb, A., 4515
Robertson, A. See Ballantine, J. A., 4779
Rodda, H. J. See Badger, G. M., 4777
Ross, T. J. See Allison, W. R., 4311
Russell, R. U., and Salmon, J. E., 4708
Ryan, A. J. See Birch, A. J., 4576, 4773
Rydon, H. N. See Crofts, P. C., 4250
Sacconi, L., Caroti, G., and Paoletti, P., 4257
Sach, G. S. See Doyle, F. P., 4458
Saint-Ruf, G. See Buu-Hoï, Ng. Ph., 4308
Salmon, J. E. See Russell, R. U., 4708
Sanderson, W. A. See Cadogan, J. I. G., 4498
Sasse, J. M. See Badger, G. M., 4777
Schofield, K. See Crabb, T. A., 4276
Schuler, B. O. G., Verbeek, A. A., and Warren, F. L., 4776
Sharma, R. K. See Mukherji, S. M., 4770
Shaw, K. B. See Johnson, A. W., 4254
Shim, J. S. See Bennett, R. N., 4508
Sinha, R. N. P. See Bradley, D. C., 4651
Smith, E. See Birch, A. J., 4471
Smith, H. See Birch, A. J., 4576, 4582, 4688, 4773, 4774
Somerfield, G. A. See Brown, B. R., 4305
Speake, R. N. See Birch, A. J., 4471
Stacey, M. See Barker, S. A., 4414
Stansfield, F., 4781
Stephen, W. I. See Belcher, R., 4454
Stirling, C. J. M., 4524, 4531
Summers, G. H. R., 4489
Sutton, L. E. See Hutchinson, M. H., 4382
Swan, G. A., and Timmons, P. S., 4669
Swan, G. A., and Wright, D., 4673
Taylor, D. A. H., 4779
Thomas, J. H. See Evans, A. G., 4563
Thompson, M. E. See Dry, L. J., 4701

XUM

Tillett, J. G. See Bunton, C. A., 4751, 4754, 4761, and Davies, E. D., 4766
Timmons, P. S. See Swan, G. A., 4669
Todd, Sir A. See Brown, D. M., 4242
Tomlinson, M. See Herbert, A. E. J., 4492
Trikojus, V. M. See Bachelard, H. S., 4541
Twomey, D. See Barry, V. C., 4495
Urch, D. S., 4767
Verbeek, A. A. See Schuler, B. O. G., 4776
Vickars, M. A. See Baddeley, G., 4665
Vig, O. P. See Mukherji, S. M., 4770
von Klemperer, M. E. See Warren, F. L., 4574
Waddington, T. C., 4340, 4783
Waind, G. M. See Martin, B., 4284
Wait, E. See Comyns, A. E., 4655
Ward, R. B. See Grant, P. M., 4635
Wardlaw, W. See Bradley, D. C., 4647, 4651, and El-Aggan, A. M., 4643
Warren, F. L., and von Klemperer, M. E., 4574
Warren, F. L., and Wright, W. G., 4696
Warren, F. L. See also Dry, L. J., 4701, and Schuler, B. O. G., 4776
Waters, W. A. See Jackson, R. A., 4632
Weitzman, P. D. J. See Brown, B. R., 4305
Whalley, W. B. See Birch, A. J., 4576, Corran, J. A., 4719, and Green, B., 4715
Whiffen, D. H. See Grant, P. M., 4635
Wilkinson, G. See Abel, E. W., 4559, and Green, M. L. H., 4314
Williams, G. H. See Chang Shih, 4403
Wilson, I. See Bunton, C. A., 4747
Woodcock, D., and Davies, B. L., 4723
Wragg, A. H. See Goldberg, A. A., 4227, 4234
Wright, D. See Swan, G. A., 4673
Wright, W. G. See Warren, F. L., 4696
Wyman, L. J. See Brooks, S. G., 4614

XUM

PAPERS ACCEPTED

Magnetochemistry. Part I. Introduction and apparatus. By B. N. Figgis and R. S. Nyholm

Magnetochemistry. Part II. The temperature-dependence of the magnetic susceptibility of bivalent cobalt compounds. By B. N. Figgis and R. S. Nyholm

Covalency and the iron group of complexes. By T. M. Dunn

The synthesis of 1-glycosylbenziminazoles. By A. J. Cleaver, A. B. Foster, and W. G. Overend

Organic compounds of zirconium. Part VI. Reactions of zirconium tetrachloride and *iso*-propoxide with fatty acids. By R. N. Kapoor and R. C. Mehrotra

Chemical applications of nuclear quadrupole resonance spectroscopy. Part II. Chloro-derivatives of maleic anhydrides, thiophen, and anilinium salts. By M. J. S. Dewar and E. A. C. Lucken

The reducing action of glycols in alkali. Part II. By Wadie Tadros, Moheb Sadek Ishak, and Edward Bassili

Solvent extraction studies. Part III. The extraction of hydrogen peroxide into tri-*n*-butyl phosphate. By D. G. Tuck

The rearrangement of nitrones. By A. H. Wragg and T. S. Stevens

Heats of combustion and molecular structure. Part VII. 1 : 3-Dioxa- and 1 : 3 : 5-trioxa-*cyclo*alkanes. By S. E. Fletcher, C. T. Mortimer, and H. D. Springall

Peroxides of elements other than carbon. Part III. The formation of boron peroxides by autoxidation. By M. H. Abraham and Alwyn G. Davies

Peroxides of elements other than carbon. Part IV. The autoxidation of tri-*sec*.-butylboron to *sec*.-butyldi-(*sec*.-butylperoxy)boron. By Alwyn G. Davies and D. G. Hare

5-Fluorotryptamine. By Z. Pelchowicz and Ernst D. Bergmann

β-Aroylpropionic acids. Part IX. Their conversion into 1 : 2-benzanthraquinones. By F. G. Baddar, Ibrahim Dewidar, and Munir Gindy

Steroids and Walden inversion. Part XLII. 5-Cholestan-4-one and some derivatives thereof. By C. W. Shoppee, M. E. H. Howden, R. W. Killick, and G. H. R. Summers

β-Aroylpropionic acids. Part X. The synthesis of β-aroyl-α- and -β-phenylpropionic acids, and their conversion into polynuclear compounds. By F. G. Baddar, Abdallah M. Fleifel, and Sayed Sherif

Nitrogenous chelate complexes of transition metals. Part I. The constitution and properties of the 1 : 10-phenanthroline complexes of tervalent gold. By C. M. Harris

Heterocyclic imines and amines. Part IX. Glutarimidine and the imidine from α-phenyl-glutaronitrile. By J. A. Elvidge, R. P. Linstead, and Ann M. Salaman

Exchange studies of certain chelate compounds of the transitional metals. Part VI. The cobalt(II)–phenanthroline system. By Peter Ellis and R. G. Wilkins

Oxidation of polyhalogeno-compounds. Part II. Photolysis and photochemical oxidation of some chlorofluoroethanes. By R. N. Haszeldine and F. Nyman

The effect of acid on the electronic spectra of organic molecules containing conjugated and unconjugated nitrogen atoms. By J. N. Murrell

Synthesis of 5-bromotryptophan and some derivatives. By D. G. Harvey

Chemistry of hop constituents. Part XIII. The hydrogenation of *iso*humulone. By P. Margaret Brown, G. A. Howard, and A. R. Tatchell

Phospholipids. Part IV. *myo*Inositol 2-phosphate. By D. M. Brown and G. E. Hall

Studies in magnetochemistry. Part III. Compounds of bivalent copper. By B. N. Figgis and C. M. Harris

The synthesis of some 9-furfurylpurines and some related heterocyclic compounds. By R. Hull

Aspects of the organic chemistry of the transition elements. Part I. Tricarbonylchromium derivatives of aromatic compounds. By B. Nicholls and M. C. Whiting

Pyrroles and related compounds. Part II. Michael addition to pyrromethenes. By A. C. Jain and G. W. Kenner

The extractives of *Quintinnia serrata*. By R. C. Cambie

Ribose and its derivatives. Part VIII. The ring structure and periodate oxidation of ribose and related polyols. By G. R. Barker and D. F. Shaw

Some aspects of the anion-exchange behaviour of uranyl nitrate in the presence of other inorganic nitrates. By J. K. Foreman, I. R. McGowan, and T. D. Smith

XUM

β-Aroyl-α-arylmethylenepropionic acids. Part I. Conversion of the lactones of β-aroyl-α-arylmethylenepropionic acids into the corresponding 1-phenylnaphthalenes. By LANSON S. EL-ASSAL and (MRS.) AWATEF H. SHEHAB

The Stobbe condensation. Part I. The cyclisation of methyl hydrogen *cis*-α-*o*-methoxyphenyl- and methyl hydrogen *cis*-α-*p*-methoxyphenyl-itaconate to the corresponding naphthalene derivatives. By A. M. EL-ABBADY and LANSON S. EL-ASSAL

Organic nitrates. Part II. Triphenylmethyl nitrate and 9-phenyl-9-fluorenyl nitrate. By G. W. H. CHEESEMAN

Organic nitrates. Part III. 9-Fluorenyl nitrate. By G. W. H. CHEESEMAN

Some reactions of xanthhydryl chloride. By G. W. H. CHEESEMAN

Ammonolysis and aminolysis of trifluoromethyl arsenicals. By W. R. CULLEN and H. J. EMELÉUS

The heptafluoropropyliodophosphines and their derivatives. By H. J. EMELÉUS and J. D. SMITH

The production of active solids by thermal decomposition. Part X. Heat treatment of the xerogels of silica. By J. F. GOODMAN and S. J. GREGG

Reactions of 1 : 2-dichloro-3 : 4-epoxybutane and related compounds. By E. G. E. HAWKINS

The interaction of *o*-chloromethylphenacyl chloride and primary amines: a novel formation of the *iso*indoline system. By I. G. HINTON, FREDERICK G. MANN, and A. VANTERPOOL

Pyranoquinolines. Part I. Application of the Kostanecki–Robinson reaction to derivatives of 3-acetyl-4-hydroxyquinoline. By K. ELLIOTT and E. TITTENSOR

The formation of aromatic hydrocarbons at high temperatures. Part V. The pyrolysis of 1-phenylbuta-1 : 3-diene. By G. M. BADGER and T. M. SPOTSWOOD

The high-temperature thermal decomposition of ammonium perchlorate. By A. K. GALWAY and P. W. M. JACOBS

The kinetics of the hydrolysis of the chlorinated methanes. By IAN FELLS and E. A. MOELWYN-HUGHES

Pteridine derivatives. Part VII. The synthesis of riboflavin 2-imine and related *iso*alloxazine 2-imines. By R. M. CRESSWELL, A. C. HILL, and H. C. S. WOOD

A quantitative study of the arylation of naphthalene by means of diazonium salts and zinc. By B. A. MARSHALL and WILLIAM A. WATERS

Hydrolysis of dialkylphosphinic fluorides and dialkyl phosphorofluoridates. By M. HALMANN

Vapour pressures of metal alkoxides. Part II. Zirconium tetra-*tert.*-butoxide and -amyloxide. By D. C. BRADLEY and J. D. SWANWICK

The structure of *cyclo*eucalenol. By J. S. G. COX, F. E. KING, and T. J. KING

The direct introduction of the diazonium group into aromatic nuclei. Part V. The action of buffered nitrous acid on aromatic hydroxy-acids. By J. M. TEDDER and G. THEAKER

Ketose–polyol interconversions by a ropy-cider organism. By S. A. BARKER, E. J. BOURNE, E. SALT, and M. STACEY

Substitution reactions with 2-methoxy- and 2-ethoxy-1-naphthylamines. By F. BELL

Preparation of symmetrical deoxybenzoins. By P. H. CARTER, J. CYMERMAN CRAIG, (MISS) RUTH E. LACK, and M. MOYLE

Polynitronaphthalenes. Part II. A quantitative study of the nitration of 1- and 2-nitronaphthalenes, and of 1 : 5-dinitronaphthalene. By E. R. WARD, C. D. JOHNSON, and (in part) L. A. DAY

Partial synthesis of the vitamins D_2 and D_3. By H. H. INHOFFEN, K. IRMSCHER, H. HIRSCHFELD, U. STACHE, and A. KREUTZER

The preparation and rearrangement of benzoates and substituted benzoates of dibromopropanols. By J. H. C. NAYLER

Oxidation of polyhalogeno-compounds. Part III. Thermal oxidation of some chlorofluoroethanes. By R. N. HASZELDINE and F. NYMAN

Reactions of tin(IV) halides with ammonia derivatives. Part III. The reaction of tin(IV) halides with aliphatic amines. By E. BANNISTER and G. W. A. FOWLES

Preparation and properties of some poly-*O*-acetylglycosyl chlorides of the " unstable " series. By W. KORYTNYK and J. A. MILLS

Modification of Hudson's rules of *iso*rotation for sugar derivatives containing highly polarisable aglycones. By W. KORYTNYK

The action of thionyl chloride on 2-methyl and 2-ethyl-1 : 3-dioxolan-2-carboxylic acid. By R. P. A. SNEEDEN

Alkyls and aryls of transition metals. Part I. Complex methylplatinum(II) derivatives. By J. CHATT and B. L. SHAW

Acyl migration in diglycerides. By A. CROSSLEY, I. P. FREEMAN, B. J. F. HUDSON, and J. H. PIERCE

XUM

Intermediates for the synthesis of optically active methyl-substituted long-chain acids. Part IV. By A. S. Bailey, V. D. Brice, M. G. Horne, and N. Polgar

The crystal and molecular structures of tiglic acid and angelic acids. Part I. Tiglic acid. By A. L. Porte and J. Monteath Robertson

The crystal and molecular structures of tiglic and angelic acids. Part II. Angelic acid. By A. L. Porte and J. Monteath Robertson

Hydrogenation of 4′-hydroxydiphenylylacetic acid. By W. H. Linnell and H. J. Smith

Preparation of 17α-acetoxy-6α-methylprogesterone. By (Miss) S. P. Barton, B. Ellis, and V. Petrow

The reaction of the 1 : 4-dichloro-2 : 3-epoxybutane with sodium methoxide. By A. W. Adams, E. G. E. Hawkins, G. F. Oldham, and R. D. Thompson

Delocalization in $p\pi$–$d\pi$ bonds. By D. P. Craig

Reaction of amino-derivatives of anthraquinone, fluorenone, and fluorene with nitrobenzene and α-nitronaphthalene. By William Bradley and F. P. Williams

The solubility behaviour of aromatic hydrocarbons in benzene. By E. McLaughlin and H. A. Zainal

The structure of zierone. Part I. The synthesis of zierazulene and (K ± 1)-methylzierazulene. By D. J. Collins

Red-seaweed polysaccharides. Part III. *Hypnea specifera*. By A. L. Clingman and J. R. Nunn

An alkaloid of *Dioscorea hispida*, Dennstedt. Part V. The degradation of dioscorinol. By J. B. Jones and A. R. Pinder

The reaction between diphenylamine and malonic esters. By R. E. Bowman, A. Campbell, and (Miss) E. M. Tanner

The solvolysis of 4 : 4-dimethylcholest-5-en-3β-yl toluene-*p*-sulphonate. By Y. M. Y. Haddad and G. H. R. Summers

11-Ethoxy-1 : 2 : 3 : 4 : 10 : 11-hexahydrofluoren-1-one. A correction. By F. H. Howell and D. A. H. Taylor

857. *Effect of Solvent Composition on the Kinetics of Reactions between Ions and Dipolar Molecules. Part I.*

By E. A. S. Cavell.

The influence of small amounts of water upon the rate at which iodide ions react with *n*-butyl bromide in acetone has been investigated. Changes in rate observed cannot, however, be satisfactorily explained in terms of changes in dielectric constant alone, even when allowance is made for incomplete dissociation of the electrolyte. A specific interaction between iodide ions and water molecules has, therefore, been postulated and its consequences considered quantitatively.

The rates of certain reactions between ions and dipolar molecules in acetone solution are known to be appreciably retarded by small amounts of water. In the reaction between bromide ions and *n*-butyl bromide, for example, Le Roux and Sugden [1] found that the rate of bromine exchange in anhydrous acetone was nine times that in acetone containing 5% by volume of water. Further increases in the proportion of water had, however, less effect on the reaction rate, which was reduced by a half when the water content was increased from 5% to 10%. Requisite experimental data for the interpretation of such changes in rate with solvent composition are not available; we therefore studied systematically the effect of small amounts of water, from 0 to 5M, on the kinetics of a typical ion–dipolar molecule reaction, namely, that between iodide ions and *n*-butyl bromide, lithium iodide providing the iodide ions because with this reagent the reacting system remained homogeneous. The reaction was followed chemically by determining the concentration of inorganic iodide. In selected experiments, the total concentration of lithium halides was also determined and found to remain constant for the duration of the exchange reaction, from which we concluded that hydrolyses and eliminations are negligible under our conditions.

Reactions between *n*-alkyl halides and halide ions are of the first order with respect to each reactant.[1,2,3] The rate of the reversible reaction $Bu^nBr + I^- \rightleftharpoons Bu^nI + Br^-$ is therefore

$$dx/dt = k_2(c - x)(d - x) - k_{-2}x^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where k_2 and k_{-2} are the rate constants for the forward and backward reactions, c and d are the initial concentrations of lithium iodide and *n*-butyl bromide, and x is the concentration of lithium bromide at time t. On integration eqn. (1) gives

$$k_2t = \frac{2{\cdot}303}{2B(K^{-1} - 1)} \log_{10} \frac{1 + x/(B - A)}{1 - x/(B + A)} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Where $A = (d + c)/[2(K^{-1} - 1)]$, $B = [(d - c)^2 + 4dc/K]^{\frac{1}{2}}/2[(K^{-1} - 1)]$, and $K = k_2/k_{-2} = x^2_\infty/[(c - x_\infty)(d - x_\infty)]$. Second-order rate constants, calculated by means of eqn. (2) from measurements at three temperatures, are summarised in Table 1; they have been corrected for thermal expansion of the solvent. Concentrations of water and of lithium iodide quoted in Table 1 have been similarly corrected and the dielectric constants ε given have been interpolated from Åkerlöf's data.[4] The initial concentration of *n*-butyl bromide was 0·035M.

Most theoretical treatments of reactions between negative ions and dipolar molecules predict that log k_2 will decrease linearly as $1/\varepsilon$ decreases.[5,6] The way in which log k_2 varies with $1/\varepsilon$ for the reaction of iodide ions with *n*-butyl bromide is illustrated in Fig. 1, the same

[1] Le Roux and Sugden, *J.*, 1939, 1279.
[2] Le Roux and Swart, *J.*, 1956, 2110.
[3] Moelwyn-Hughes, *Trans. Faraday Soc.*, 1949, **45**, 167.
[4] Åkerlöf, *J. Amer. Chem. Soc.*, 1932, **54**, 4125.
[5] Laidler and Landskroener, *Trans. Faraday Soc.*, 1956, **52**, 200.
[6] Moelwyn-Hughes, "Kinetics of Reactions in Solution," Oxford University Press, 2nd edn., p. 120.

XUM

pattern being observed at different temperatures and with different initial concentrations of electrolyte. It is seen that for water concentrations exceeding 2M, the variation of log k_2 with $1/\varepsilon$ is almost linear, although no such simple relation is shown at water concentrations less than this. Kacser [7] has, however, developed a theory which takes into

TABLE 1. *Rate constants (k_2 in l. mole^{-1} sec.$^{-1}$) calculated from eqn. (2).*

[H_2O]	10^2c	10^3k_2	ε	[H_2O]	10^2c	10^3k_2	ε
			Temp. = 19·80°				
0	1·76	1·016	19·58	0·496	1·77	0·545	20·14
0·071	1·76	0·873	19·66	0·922	1·77	0·426	20·62
0·082	1·76	0·850	19·67	1·86	1·78	0·283	21·68
			Temp. = 30·35°				
0	1·69	3·28	18·64	0·483	1·67	1·69	19·16
0·015	1·68	3·22	18·66	0·928	1·67	1·29	19·63
0·061	1·69	2·84	18·70	1·86	1·67	0·842	20·63
0·096	1·64	2·65	18·74	2·98	1·68	0·638	21·80
0·246	1·67	2·15	18·90	4·96	1·70	0·434	23·88
			Temp. = 40·03°				
0	1·69	8·74	17·80	0·906	1·71	3·44	18·74
0·084	1·69	7·28	17·89	1·84	1·67	2·29	19·71
0·247	1·70	5·61	18·06	2·94	1·69	1·69	20·83
0·472	1·70	4·52	18·29	4·84	1·72	1·13	22·79
0	0·802	9·59	17·80	0·481	0·789	5·25	18·30
0·091	0·789	7·56	17·89	0·945	0·797	3·89	18·78
0·254	0·792	6·51	18·06	1·82	0·811	2·64	19·70

account the angular dependence of the electrostatic energy of interaction between an ion and a dipole. This theory requires that log (k_2/ε) shall be inversely proportional to the dielectric constant, but this is also unsuccessful in dealing with our rate constants.

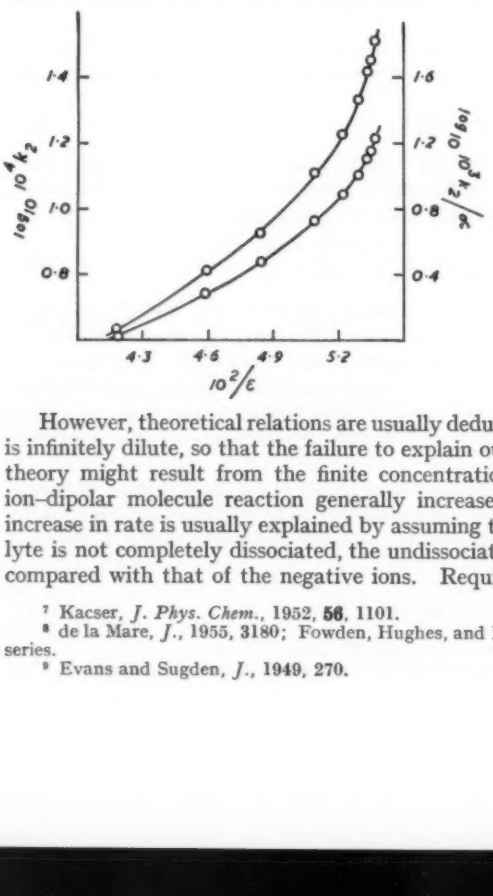


FIG. 1. *Plots of* log 10^4k_2 *(upper curve) and* log$10^3k_2/\alpha$ *(lower curve) against the reciprocal of the dielectric constant for* 30·35°.

However, theoretical relations are usually deduced by assuming that the reacting system is infinitely dilute, so that the failure to explain our kinetic results in terms of a particular theory might result from the finite concentrations used. Now the specific rate of an ion–dipolar molecule reaction generally increases with increasing dilution [8,9] and the increase in rate is usually explained by assuming that, at finite concentrations, the electrolyte is not completely dissociated, the undissociated molecules reacting at a rate negligible compared with that of the negative ions. Requisite conductances for the calculation of

[7] Kacser, *J. Phys. Chem.*, 1952, **56**, 1101.
[8] de la Mare, *J.*, 1955, 3180; Fowden, Hughes, and Ingold, *ibid.*, p. 3187; and other papers in this series.
[9] Evans and Sugden, *J.*, 1949, 270.

the degree of dissociation α of lithium iodide in mixtures of acetone and water are not available, but calculations by Evans and Sugden [9] for lithium bromide in dry acetone suggest that in this solvent the proportion of lithium iodide dissociated into ions is likely to be small. If the remainder of the electrolyte is in the form of ion pairs then a dissociation constant K_d for the equilibrium between free ions and ion pairs can be calculated by means of

$$-\log_{10} K_d = 13{\cdot}547 - 3\log_{10}(\varepsilon T) + \log_{10} Q(b) \quad . \quad . \quad . \quad . \quad (3)$$

where $b = 10^4(6{\cdot}02/\varepsilon T)$ and $Q(b) = \int_2^b e^q q^{-4}\,dq$, numerical values of which can be obtained from tables.[10] Dissociation constants have been calculated at two temperatures for the range of dielectric constants covered in our experiments, and from these dissociation constants, shown in Table 2, the corresponding degrees of dissociation of the electrolyte have been obtained. Experimental rate constants corrected for the effect of ion association by dividing each of them by the appropriate value of α are also shown in Table 2. The plot log k_2/α against $1/\varepsilon$ (Fig. 1) is not straight, however, so that ion association is not solely responsible for the absence of the linear relation between log k_2 and $1/\varepsilon$ required by the theories.

TABLE 2. *Dissociation constants of lithium iodide calculated from eqn.* (3), *and rate constants corrected for ion-association.*

$T = 303{\cdot}5°$ K									
ε	18·64	18·70	18·74	18·90	19·16	19·63	20·63	21·80	23·88
10^4K_d	8·04	8·26	8·41	9·10	10·19	12·56	18·2	26·8	48·0
$10^3k_2/\alpha$	16·73	14·34	13·12	10·34	7·75	5·40	3·01	1·95	1·061
$T = 313{\cdot}2°$ K									
ε	17·80	17·89	18·06	18·29	18·74	19·71	20·83	22·79	
10^4K_d	7·05	7·40	8·04	8·95	11·02	16·33	24·2	43·7	
$10^3k_2/\alpha$	47·5	38·7	28·8	22·05	15·36	8·48	5·38	2·87	

Many ion–dipolar molecule reactions are subject also to a kinetic salt effect [11] which arises because the expressions for the activity coefficients of the reactants and for the activity coefficient of the transition state contain terms which are proportional to the ionic strength and which are not necessarily equal. In such cases log k_2 may also be proportional to the ionic strength, the proportionality constant being a function of the dielectric constant of the solvent. Laidler and Landskroener [5] consider that this proportionality constant should be inversely proportional to the dielectric constant, so that such a salt effect cannot explain the failure of the specific rate of the reaction studied to change with the dielectric constant in the way expected from theory. In any case, when rate constants, obtained with different initial electrolyte concentrations and corrected for ion association, are compared, the kinetic salt effect appears to be small.

The difficulty of accounting for the effect of small amounts of water upon the specific rate of the reaction between iodide ions and *n*-butyl bromide might be resolved by assuming water to play a more direct part in the reaction than simply increasing the dielectric constant. Suppose, for example, that an equilibrium $I^- + H_2O \rightleftharpoons (I,H_2O)^-$ is rapidly established. For our purpose the nature of the interaction need not be specified, although in a medium having a dielectric constant of 20, the electrostatic energy of interaction between an iodide ion and a water molecule will be about 1500 cal. mole^{-1}. This should be sufficiently large for the entity $(I,H_2O)^-$, if it exists, to persist through a number of collisions with other solvent molecules at ordinary temperatures. If, in a medium of dielectric constant ε_0, the specific rates with which I^- and $(I,H_2O)^-$ react with *n*-butyl bromide are k_0 and k_∞ respectively then, when the concentration of water is *s*, the rate

[10] Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Co. New York, 2nd edn., p. 190.
[11] Ref. 6, p. 130.

constant k_s, obtained by correcting the observed value to dielectric constant ε_0, will be related to k_0 and k_∞ by the expression

$$k_s = k_0(1 - y) + k_\infty y \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where y is the fraction of the total iodide ion present as $(I,H_2O)^-$ at the concentration of water concerned.

It follows from eqn. (4) that, provided the concentration of $(I,H_2O)^-$ is always much less than s, the quotient $(k_0 - k_s)/(k_s - k_\infty)$ will be directly proportional to s. In the computation of this quotient for different concentrations of water, however, the experimental rate constants, even when corrected for ion-association, may not be used directly, because each value of k_2 corresponds to a different dielectric constant and the specific rate of an ion–dipolar molecule reaction will not be independent of the dielectric constant of the solvent. We have, therefore, corrected each experimental rate constant to a standard dielectric constant ε_0, namely, that of dry acetone at the temperature concerned, by

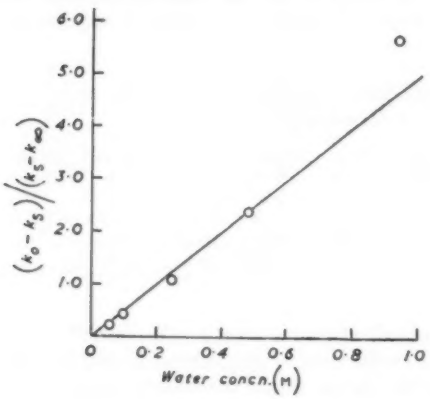


FIG. 2. *Plot of* $(k_0 - k_s)/(k_s - k_\infty)$ *against water concentration for* 30·35°.

assuming that there is a linear relation between log k_2 and $1/\varepsilon$. On the basis of the equilibrium postulated above, however, this assumption implies that for the reactions of I^- and $(I,H_2O)^-$ with *n*-butyl bromide, the coefficients $\partial \log k/\partial(1/\varepsilon)$ have the same numerical value. This is clearly an approximation. Nevertheless, the fact that for the type of reaction considered here, an approximately linear relation between log k and $1/\varepsilon$ has been observed in a series of pure hydroxylic solvents [12,13] suggests that if ionic species similar to that postulated exist in these solvents, then this approximation may not involve too serious an error in practice. Thus, for any concentration of water, k_s can be calculated from the corresponding value of k_2 by means of

$$\log k_s = \log k_2 + m(1/\varepsilon_0 - 1/\varepsilon_s) \, . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where ε_s is the dielectric constant appropriate to the concentration of water chosen and m is the slope of the linear portion of the log k_2–$1/\varepsilon$ curve, *i.e.*, we have assumed that the value of $\partial \log k/\partial(1/\varepsilon)$ for the reaction of $(I,H_2O)^-$ with the alkyl halide may be used to correct the rate constants of both the reactions postulated.

Values of k_s calculated from eqn. (5) for 30·35° and 40·03° are recorded in Table 3; k_∞ is obtained by extrapolating the linear part of the log k_2–$1/\varepsilon$ curve to $1/\varepsilon_0$ and k_0 is the value of k_2 for the dry solvent. In Fig. 2, $(k_0 - k_s)/(k_s - k_\infty)$ has been plotted against

[12] Swart and Le Roux, *J.*, 1957, 406.
[13] Heyding and Winkler, *Canad. J. Chem.*, 1951, **29**, 790.

concentration of water. Most of the points lie close to the same straight line in satisfactory agreement with the requirements of the equilibrium postulated above, although in view of the assumptions this agreement cannot be taken as establishing the correctness of the initial hypothesis. Deviations from linearity are, however, observed at the highest water concentrations, but these may be due to the increasing sensitivity of $(k_0 - k_s)/(k_s - k_\infty)$ to errors in k_s as the value of the latter approaches that of k_∞.

TABLE 3. *Values of k_s calculated by means of eqn.* (5).

Temp. = 30·35°. m = 43·5. 10^3k_0 = 3·28. 10^3k_∞ = 1·41.								
$[H_2O]$	0	0·061	0·096	0·246	0·483	0·928	1·86	2·98	4·96
10^3k_s	3·28	2·89	2·73	2·32	1·96	1·69	1·42	1·39	1·41
Temp. = 40·03°. m = 44·5. 10^3k_0 = 8·74. 10^3k_∞ = 3·97.								
$[H_2O]$	0	0·084	0·247	0·472	0·906	1·84	2·94	4·84	
10^3k_s	8·74	7·50	6·10	5·28	4·59	4·00	3·91	3·99	

The correction for ion association has been omitted because of the uncertainties involved in the evaluation of the dissociation constants given in Table 2. Nevertheless, had this correction been applied then the result obtained would have been similar to that illustrated in Fig. 2 for the uncorrected rate constants.

The Arrhenius parameters shown in Table 4 were calculated from the experimental rate constants (Table 1) by the method of least squares. Apart from an occasional irregularity, the pre-exponential factor A_2 decreases continuously as the water concentration is increased, although it is most sensitive to changes in water concentration when the

TABLE 4. *Parameters of the equation $k_2 = A_2 \exp(-E_A/RT)$ (with A_2 in l. mole^{-1} sec.$^{-1}$, and E_A in kcal. mole^{-1}).*

$[H_2O]$ *	0	0·086	0·246	0·484	0·919	1·86	2·96	4·90
$\log_{10}A_2$	11·5	11·3	10·8	11·0	10·7	10·5	10·5	10·1
E_A	19·4	19·2	18·7	19·1	18·8	18·9	19·0	18·7

* Average values, calculated from water concentrations appropriate to the rate constants used in evaluating the Arrhenius parameters concerned.

solvent is most nearly dry. An increase in water concentration has, however, little effect on the energy of activation E_A, the maximum change in which is 700 cal. mole^{-1}.

EXPERIMENTAL

Lithium iodide was crystallised from water and dried by heating *in vacuo* over phosphoric oxide for 1 hr. at 60° and then at 120° until no further loss in weight occurred. *n*-Butyl bromide was washed with acid, then alkali, and finally with water. It was dried over phosphoric oxide and then fractionated through a column packed with glass helices; b. p. 101·2—101·8°/760 mm., n_D^{15} 1·4423.

"AnalaR" acetone was refluxed with solid potassium permanganate and lime for several hours, then distilled and kept over anhydrous potassium carbonate for some days. It was then fractioned through a column packed with metal-gauze rings, the fraction of b. p. 56·0—56·2° being collected. Sufficient of this acetone for a kinetic run was distilled under reduced pressure over phosphoric oxide [14] to remove the last traces of water, the final concentration of which was about 0·005M (Karl Fischer). In all subsequent operations the solvent was protected from the atmosphere by guard tubes containing phosphoric oxide and silica gel.

Solutions of known concentration were prepared by distilling sufficient dried acetone into two calibrated vessels, each of which contained a weighed amount of one reactant and, where appropriate, a known weight of water. 5 ml. aliquot portions of each reactant solution were transferred with an automatic pipette into a series of glass bulbs at −80°. The bulbs were sealed off after they had been charged with both solutions and were kept at −80° until required. To carry out a kinetic run, sufficient bulbs were transferred simultaneously to a thermostat,

[14] Timmermans and Gillo, *Roczniki Chem.*, 1938, **18**, 812.

each bulb being shaken several times during about 2 min. to ensure that the contents had reached thermostat temperature. To provide a time zero, two bulbs were then withdrawn and cooled rapidly to −80° to stop the reaction. The concentration of iodide ion present in each was determined by Lang's iodine cyanide method by use of 0·005M-potassium iodate. Further bulbs were withdrawn after suitable intervals until equilibrium had been attained; these were treated similarly. In some cases the total halide-ion concentration was determined instead, by means of Volhard's method with 0·02N-ammonium thiocyanate.

THE UNIVERSITY, SOUTHAMPTON. [*Received, April 29th*, 1958.]

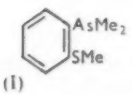
---

858. *Metallic Complexes of Dimethyl-o-methylthiophenylarsine. Part I. Complexes of Nickel and Palladium.**

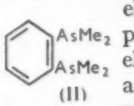
By STANLEY E. LIVINGSTONE.

The preparation of dimethyl-*o*-methylthiophenylarsine (I), which can function as a chelating ligand, is described. Bivalent nickel forms complexes, $Ni(chel)_2X_2$ [chel = the arsine (I); X = Cl, Br, I], which are paramagnetic and poor conductors in nitrobenzene. Bivalent palladium forms complexes of three types: (*a*) Pd chel X_2, (X = Cl, Br, I, SCN); (*b*) $Pd(chel)_2X_2$, (X = Cl, Br, I); (*c*) $Pd(chel)_2(ClO_4)_2$. Complexes of type (*a*) are non-electrolytes in nitrobenzene. Molecular weights, conductivities, and absorption spectra indicate that in non-aqueous solutions of complexes of type (*b*) there is an equilibrium $[Pd(chel)_2X]X \rightleftharpoons [Pd\ chel\ X_2] + chel$. The compound $[Pd(chel)_2](ClO_4)_2$ has the conductivity expected for a bi-univalent electrolyte in nitrobenzene.

THE chelating ligand *o*-phenylenebisdimethylarsine (II) was first prepared by Chatt and Mann,[1a] who described some of its complexes with palladium [1b]; Nyholm and his co-workers [2] have shown that it forms stable complexes with a large number of transition elements. The metal atom in some of these complexes displays an unusually high valency,[3] while in complexes of elements with a d^8-configuration (Pd^{II}, Pt^{II}, Au^{III}) the metal atom often exhibits an unusually high co-ordination number.[4,5] Recently, a number of similar *o*-phenylene ligands containing nitrogen, phosphorus, sulphur, or arsenic have been prepared and their metal chelates examined.[6,7]



(I)



(II)

Dimethyl-*o*-methylthiophenylarsine (I), a colourless liquid, was synthesized in order to study the types of transition-metal complex to which it would give rise. Chelate groups containing bicovalent sulphur are much less effective than tertiary arsines in forming stable complexes,[7] but this compound (I) contains a sulphur and an arsenic atom, each capable of forming a co-ordinate bond to form a five-membered ring, so it is of interest to compare its complexes with those of the diarsine (II).

The arsine (I) with nickel halides in alcoholic solution gives crystalline derivatives (Table 1) which are decomposed by water. The iodo-nickel complex is soluble in hot acetone to give a brown solution, changed to yellow by addition of a large excess (>100

* This work was briefly reported in *Chem. and Ind.*, 1957, 143.

[1] Chatt and Mann, *J.*, 1939, (*a*) 610; (*b*) 1622.

[2] For a full list of references see Nyholm and Sutton, *J.*, 1958, 560.

[3] (*a*) Nyholm, *J.*, 1950, 2061; (*b*) *idem*, *J.*, 1951, 2602; (*c*) Nyholm and Parish, *Chem. and Ind.*, 1956, 470.

[4] Harris, Nyholm, and Stephenson, *Rec. Trav. chim.*, 1956, **75**, 687.

[5] Harris and Nyholm, *J.*, 1956, 4375; 1957, 63.

[6] Jones and Mann, *J.*, 1955, 4472; Mann and Stewart, *J.*, 1955, 1269; Hart and Mann, *Chem. and Ind.*, 1956, 574; *J.*, 1957, 3939; Mann and Watson, *J.*, 1957, 3945, 3950; Cochran, Hart, and Mann, *J.*, 1957, 2816.

[7] Backhouse, Foss, and Nyholm, *J.*, 1957, 1714; Backhouse and Nyholm, personal communication.

fold) of the arsine (I). The only compound isolated from this solution was the original nickel complex, $Ni(chel)_2I_2$. This colour change and the conductivities of the nickel

TABLE 1. *Nickel complexes of dimethyl-o-methylthiophenylarsine.*

Compound	Colour	Magnetic moment (B.M.)	Molecular cond. in $PhNO_2$ (10^{-3}M) at 25° (mho)	Molecular cond. in $PhNO_2$ (2×10^{-4}M) containing 800-fold excess of (I) at 25° (mho)
$Ni(chel)_2Cl_2$ ...	Blue	3·08	0	0·9
$Ni(chel)_2Br_2$ ...	Green	3·20	1·0	8·6
$Ni(chel)_2I_2$ ...	Brown	3·05	5·8	30·5

complexes in nitrobenzene solution containing a large excess of arsine suggest the formation in solution of the unstable ion $[Ni(chel)_3]^{2+}$:

$$Ni(chel)_2X_2 + chel \rightleftharpoons [Ni(chel)_3]^{2+} + 2X^-$$

The equilibrium lies farther to the right when X = I, as might be expected in a non-aqueous solvent, if we regard the order of relative strengths of the nickel–halogen bonds to be Cl > Br > I.

The substitution of one $-AsMe_2$ group by $-SMe$ in the ligand (II) markedly alters the properties of the bivalent nickel complexes. Those of *o*-phenylenebisdimethylarsine (II) are diamagnetic and uni-univalent electrolytes in nitrobenzene [3a, 8] while those of dimethyl-*o*-methylthiophenylarsine (I) are paramagnetic and poor conductors in this solvent.

Bivalent palladium forms with the arsine (I) complexes which are non-electrolytes in nitrobenzene. In these complexes, Pd chel X_2 (Table 2), the palladium atom has its usual covalency of four. Treatment of the complex Pd chel X_2 (X = Cl, Br, I) with one molar equivalent of the arsine (I) in aqueous acetone, followed by concentration and cooling of the solution, causes deposition of crystals of the corresponding complex, $Pd(chel)_2X_2$. The chloro-compound with perchloric acid in aqueous solution gives the perchlorate, $Pd(chel)_2(ClO_4)_2$, which can be recrystallized from water (Table 2).

TABLE 2. *Molecular conductivities of palladium complexes of dimethyl-o-methylthiophenylarsine in nitrobenzene at* 25°.

Compound	Colour	Molar concn.	Molecular cond. (mho)
Pd chel Cl_2	Pale yellow	10^{-3}	0·1
Pd chel Br_2	Yellowish-orange	10^{-3}	0·1
Pd chel I_2	Deep red	10^{-3}	0·1
Pd chel $(SCN)_2$	Yellowish-orange	10^{-3}	0·1
$Pd(chel)_2Cl_2$	Deep orange	10^{-3}	4·6
$Pd(chel)_2Br_2$	Orange-brown	10^{-4}	4·5
$Pd(chel)_2I_2$	Reddish-brown	10^{-4}	4·6
$Pd(chel)_2(ClO_4)_2$	Yellowish-orange	10^{-4}	57·4

The conductances of nitrobenzene solutions of the compounds $Pd(chel)_2X_2$ are increased on the addition of the arsine (I). The molecular conductivity ($\Lambda_{10,000}$) of the compound $Pd(chel)_2Cl_2$ was measured at 25° in nitrobenzene containing varying amounts of the arsine (I). The molecular conductivity reaches a limiting value (25—26 mho) when the arsine (I) is present in concentrations above 300-fold molar excess. The molecular conductivities ($\Lambda_{10,000}$) of the corresponding bromo- and iodo-complexes $Pd(chel)_2Br_2$ and $Pd(chel)_2I_2$ at 25° in nitrobenzene containing the arsine (I) in 800-fold excess were 27·2 and 25·5 mho, respectively.

Molecular weights of the chloro- and iodo-complexes are listed in Table 3.

The absorption spectra of the iodo-complexes, shown in Fig. 1, indicate that $Pd(chel)_2I_2$ dissociates to a considerable extent in acetone to Pd chel I_2. In the presence of a large excess of the chelate (I) the compound $Pd(chel)_2I_2$ does not yield any appreciable concentration of Pd chel I_2 in solution.

[8] Harris, Nyholm, and Stephenson, *Nature*, 1956, **177**, 1127.

TABLE 3. *Molecular weights, M, and van t'Hoff factors, i, determined cryoscopically in nitrobenzene.*

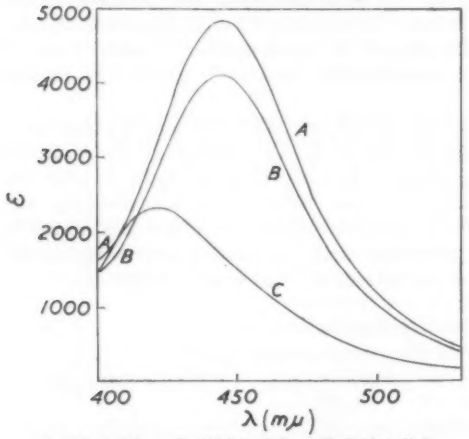
Compound	Concn. (% w/w)	*M* (obs.)	*M* (calc.)	*i*
$Pd(chel)_2Cl_2$	0·73	385	634	1·65
$Pd(chel)_2I_2$	1·23	499	817	1·64

The evidence from conductivity measurements, molecular weight determinations, and absorption spectra indicates that in acetone and nitrobenzene there exists an equilibrium:

$$[Pd(chel)_2X]^+X^- \rightleftharpoons [Pd\ chel\ X_2] + chel$$

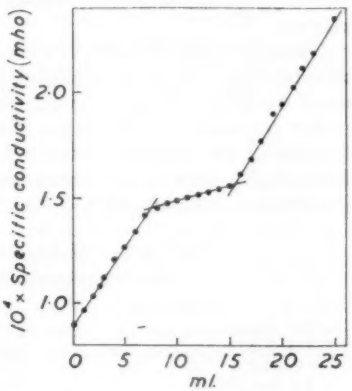
This does not necessarily mean that in these solvents the palladium atom is quinquecovalent, since the sixth position is probably occupied by a molecule of the solvent. The conductivity of the compound $Pd(chel)_2(ClO_4)_2$ indicates that the palladium atom is quadricovalent, as might be expected since the perchlorate ion shows no tendency to co-ordinate to palladium.[9]

FIG. 1. *Absorption spectra of iodo-complexes* (2×10^{-4}M-*solutions in acetone*).



A, Pd chel I_2. *B*, $Pd(chel)_2I_2$. *C*, $Pd(chel)_2I_2$ with 800-fold excess of chel.

FIG. 2. *Conductimetric titration of* $Pd(chel)_2(ClO_4)_2$ (150 *ml. of* 5×10^{-4}M-*solution*) *with* 10^{-2}M-*sodium iodide in acetone at* 25° (*corrected for dilution*). *Theoretical end points* 7·5 *ml. and* 15·0 *ml.*



Conductimetric titration of $[Pd(chel)_2](ClO_4)_2$ with iodide ions in acetone solution (Fig. 2) shows that two iodide ions react with the complex. The absorption spectrum of the solution at the completion of the titration displays a maximum at 443·7 mμ with the same value for the extinction coefficient ($\log \varepsilon = 3{\cdot}61$) as was obtained for $Pd(chel)_2I_2$ in acetone.

Bivalent palladium can possess a co-ordination number greater than four; the compound $Pd(diarsine)_2I_2$ [diarsine = (II)] possesses a distorted octahedral configuration in the solid state [8] and exists in nitrobenzene as a uni-univalent electrolyte.[5] The chloropalladate(II) ion, having more than four chlorine atoms per palladium atom, exists in aqueous solution,[10] and the ion $[PdBr_6]^{4-}$ exists in nitrobenzene solutions containing the tetrabromopalladate(II) ion, $[PdBr_4]^{2-}$, and bromide ion.[11] The crystalline compounds $Pd(chel)_2X_2$ show marked differences in colour from the compounds Pd chel X_2. In the solid state the former undoubtedly possess a distorted octahedral configuration, similar to that found for $Pd(diarsine)_2I_2$.

[9] Livingstone, *J.*, 1957, 5091.
[10] Sundaram and Sandell, *J. Amer. Chem. Soc.*, 1955, **77**, 855.
[11] Harris, Livingstone, and Reece, *Austral. J. Chem.*, 1957, **10**, 282.

XUM

The ligand (I) appears to be less effective than *o*-phenylenebisdimethylarsine (II) in stabilizing sexicovalent palladium. A detailed discussion of the type of bonding present in sexicovalent palladium complexes has been published.[5] On ligand-field theory the filled d_{z^2} orbital of the palladium atom projects along the line of approach to the two vacant octahedral sites. Harris and Nyholm [5] postulate double bonding between palladium and two of the four arsenic atoms in the compounds $Pd(diarsine)_2X_2$, thereby causing the palladium atom to possess a residual positive charge. If we consider similar π-bonding to occur in the complexes $Pd(chel)_2X_2$, the greater electronegativity of sulphur (2·5) than of arsenic (2·0) [12] will produce a lower residual positive charge on the palladium atom. Accordingly, a greater repulsion will be exerted along the *z*-axis on any incoming negatively charged ligands in the fifth and sixth octahedral positions, leading to lower stability of the palladium complexes of ligand (I) than of ligand (II).

Experimental

Dimethyl-o-methylthiophenylarsine.—*o*-Methylthioaniline (100 g.), prepared from *o*-mercaptoaniline,[13] was treated with 5M-sulphuric acid (400 ml.). This solution was diazotized at 10° by the addition of a solution of sodium nitrite (58 g.), then 5M-sodium hydroxide (215 ml.) was added. The diazotized solution was treated quickly below 10° with a solution containing arsenious oxide (14 g.), sodium hydroxide (120 g.), and copper sulphate pentahydrate (25 g.) in water (1 l.). The mixture was acidified with acetic acid and filtered. The filtrate was concentrated to 800 ml. and made acid to Congo Red paper with hydrochloric acid. The crude product was filtered off and recrystallised from 50% alcohol, yielding pure *o-methylthiophenylarsonic acid* (63 g.), m. p. 154—154·5 (Found: C, 34·0; H, 3·8; $C_7H_9O_3SAs$ requires C, 33·9; H, 3·7%). Sulphur dioxide was passed for several hours into a solution of the arsonic acid (63 g.) in 7M-hydrochloric acid. The resulting crystalline precipitate contained water, which was removed by dissolution of the crude product in benzene and separation of the aqueous layer. The benzene solution was dried (Na_2SO_4) and, on being concentrated and cooled, yielded colourless crystals of *dichloro-o-methylthiophenylarsine* (52 g.), m. p. 66—67° (Found: C, 31·3; H, 2·6. $C_7H_7Cl_2SAs$ requires C, 31·3; H, 2·6%). The dichloroarsine (62 g.) was dissolved in ether (500 ml.) and treated with an ethereal solution of the Grignard reagent from methyl iodide (78·5 g.) and magnesium (13 g.). The yellow addition product was decomposed with ammonium chloride solution. The ether layer was separated, dried, and evaporated to give a crude oil (54 g.) which was distilled under reduced pressure (coal gas), yielding *dimethyl-o-methylthiophenylarsine* (42·7 g.), b. p. 122—124°/3·5 mm., n_D^{25} 1·6278 (Found: C, 47·2; H, 5·8. $C_9H_{13}SAs$ requires C, 47·4; H, 5·7%).

Dichlorobisdimethyl-o-methylthiophenylarsinenickel(II).—Dimethyl-*o*-methylthiophenylarsine (1 g.) in alcohol (5 ml.) was added to a warm solution of anhydrous nickel chloride (0·59 g.) in alcohol (10 ml.). On cooling, the solution deposited blue crystals of the *nickel complex*; these were filtered off and washed with alcohol (Found: C, 37·1; H, 4·8; Cl, 12·0. $C_{18}H_{26}Cl_2S_2As_2Ni$ requires C, 36·9; H, 4·5; Cl, 12·1%).

Dibromobisdimethyl-o-methylthiophenylarsinenickel(II).—Prepared from anhydrous nickel bromide as for the chloro-complex, the bright green crystals of the *compound* were filtered off and washed with alcohol and a little acetone (Found: C, 31·8; H, 4·0; Br, 23·6; N, 8·9. $C_{18}H_{26}Br_2S_2As_2Ni$ requires C, 32·0; H, 3·9; Br, 23·7; Ni, 8·7%).

Di-iodobisdimethyl-o-methylthiophenylarsinenickel(II).—Dimethyl-*o*-methylthiophenylarsine (0·8 g.) in alcohol (5 ml.) was added to a hot solution of nickel perchlorate hexahydrate (1·3 g.) and lithium iodide (0·5 g.) in alcohol. The dark brown crystals of the *iodo-complex* were filtered off and washed with a little alcohol (Found: C, 28·4; H, 3·4; I, 32·9; Ni, 8·0. $C_{18}H_{26}I_2S_2As_2Ni$ requires C, 28·1; H, 3·4, I, 33·0; Ni, 7·6%).

Dichloro(dimethyl-o-methylthiophenylarsine)palladium(II).—Dimethyl-*o*-methylthiophenylarsine (2·7 g.) in alcohol was added to potassium chloropalladate(II) (3·9 g.) in water (75 ml.). The yellow precipitate was filtered off, washed with water, and recrystallized from acetone (450 ml.) containing 10% of water, to yield pale yellow crystals of the *complex* (4·1 g.) (Found: C, 26·5; H, 3·2; Cl, 17·5; Pd, 26·5. $C_9H_{13}Cl_2SAsPd$ requires C, 26·6; H, 3·2; Cl, 17·5; Pd, 26·3%).

[12] Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, 2nd edn., 1940, p. 60.
[13] Livingstone, *J.*, 1956, 437.

Dibromo(dimethyl-o-methylthiophenylarsine)palladium(II).—An aqueous solution of potassium bromopalladate(II) (1·1 g.) was treated with dimethyl-*o*-methylthiophenylarsine (0·5 g.) in alcohol. The orange precipitate was filtered off, washed with water, and recrystallized from 90% acetone to give orange crystals of the *bromo-complex* (0·44 g.) (Found: C, 22·4; H, 2·6; Br, 32·1; Pd, 22·0. $C_9H_{13}Br_2SAsPd$ requires C, 21·9; H, 2·6; Br, 32·3; Pd, 21·6%).

Di-iodo(dimethyl-o-methylthiophenylarsine)palladium(II).—The chloro-complex (0·9 g.) was dissolved in hot 90% acetone (200 ml.) and added to lithium iodide (5 g.) in hot 90% acetone (50 ml.). The deep red solution was concentrated to 100 ml. and cooled to give red crystals of the *compound*, which was recrystallized from 90% acetone (yield, 1·0 g.) (Found: C, 18·3; H, 2·1; I, 43·0; Pd, 18·2. $C_9H_{13}I_2SAsPd$ requires C, 18·4; H, 2·2; I, 43·1; Pd, 18·1%).

Dithiocyanato(dimethyl-o-methylthiophenylarsine)palladium(II).—The chloro-complex (0·4 g.) was dissolved in hot 90% acetone (85 ml.) and added to a solution of lithium thiocyanate (2 g.) in aqueous acetone. The reddish-orange solution, after being concentrated to 40 ml. and cooled, deposited yellowish-orange crystals of the *compound*, which was recrystallized from aqueous acetone (yield, 0·25 g.) (Found: C, 29·6; H, 3·1; N, 6·4; Pd, 23·7. $C_{11}H_{13}N_2S_3AsPd$ requires C, 29·3; H, 2·9; N, 6·2; Pd, 23·6%).

Dichlorobisdimethyl-o-methylthiophenylarsinepalladium(II).—Dimethyl-*o*-methylthiophenylarsine (0·55 g.) was added to a suspension of dichloro(dimethyl-*o*-methylthiophenylarsine)-palladium(II) (1 g.) in 90% acetone (100 ml.) to give a deep orange solution. The solution was evaporated on a steam-bath to a viscous gum, which, when scratched, crystallised. The deep orange crystals of the *compound* were triturated with ether and dried *in vacuo* (P_2O_5) (yield 1·20 g., m. p. 88°) (Found: C, 32·6; H, 4·1; Cl, 11·0; Pd, 16·6. $C_{18}H_{26}Cl_2As_2Pd$ requires C, 34·1; H, 4·2; Cl, 11·2; Pd, 16·8%). The compound is hygroscopic.

Dibromobisdimethyl-o-methylthiophenylarsinepalladium(II).—Dimethyl-*o*-methylthiophenylarsine (0·4 g.) was added to dibromo(dimethyl-*o*-methylthiophenylarsine)palladium(II) (0·67 g.) in 90% acetone. The solution was concentrated to small bulk (8 ml.) and kept overnight; orange crystals of the *complex* separated. The crystals were filtered off, washed with ether, and dried *in vacuo* (P_2O_5) (Found: Br, 21·8; Pd, 14·7. $C_{18}H_{26}Br_2S_2As_2Pd$ requires Br, 22·1; Pd, 14·7%).

Di-iodobisdimethyl-o-methylthiophenylarsinepalladium(II).—Dimethyl-*o*-methylthiophenylarsine (1·25 g.) was added to a suspension of di-iodo(dimethyl-*o*-methylthiophenylarsine)-palladium(II) (1 g.) in 80% acetone (150 ml.), producing a red solution, which was concentrated to 50 ml. and cooled. The solution deposited brownish-orange crystals of the pure *compound* which were filtered off, washed with ether, and dried (yield, 0·90 g.) (Found: C, 26·7; H, 3·2; I, 31·0; Pd, 13·0. $C_{18}H_{26}I_2S_2As_2Pd$ requires C, 26·5; H, 3·2; I, 31·0; Pd, 13·0%).

Bisdimethyl-o-methylthiophenylarsinepalladium(II) *Perchlorate.*—Dichlorobisdimethyl-*o*-methylthiophenylarsinepalladium(II) in hot water (15 ml.) was treated with 72% perchloric acid (2 ml.). The resulting yellow precipitate was filtered off, washed with a little water, and recrystallised from water, washed with acetone, and dried (yield of the pure *compound*, 0·2 g.) (Found: C, 28·1; H, 3·4; Pd, 13·9. $C_{18}H_{26}O_8Cl_2S_2As_2Pd$ requires C, 28·4; H, 3·4; Pd, 14·0%).

Magnetic-susceptibility Measurements.—The magnetic susceptibilities of the nickel complexes were measured on the solid compounds at room temperature. The values for the diamagnetic corrections are taken from Selwood.[14] The magnetic data are as follows:

Compound	T(°K)	$10^6\chi_g$	$10^6\chi_M$	$10^6\chi_M$ (corr. for diamagnetism)	$\mu_{eff.}$ (B.M.)
$Ni(chel)_2Cl_2$	288	6·35	3722	4064	3·08
$Ni(chel)_2Br_2$	295	5·91	3997	4360	3·20
$Ni(chel)_2I_2$	298	4·49	3455	3846	3·05

Analyses for carbon, hydrogen, and nitrogen were carried out by Dr. E. Challen of the microanalytical laboratory of this University.

Department of Inorganic Chemistry,
New South Wales University of Technology,
Sydney, Australia.

[*Received, May 21st*, 1958.]

[14] Selwood, "Magnetochemistry," Interscience Publ. Inc., New York, 1943, p. 52.

XUM

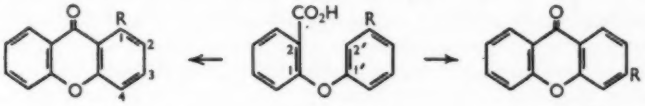
859. *Xanthones: Cyclisation of 3′-Substituted 2-Carboxydiphenyl Ethers.*

By A. A. Goldberg and A. H. Wragg.

Cyclisation of 3′-substituted 2-carboxydiphenyl ethers has been studied in order to determine the effect of the 3′-substituent on the direction of ring closure. For substituents having a strong $-I$, $-M$ effect (NO_2, CO_2H, CN) the ratio of products respectively formed by cyclisation on to the 2′- and the 6′-position is of the order of 80 : 20. For substituents with a strong $-I$, $+M$ effect (NHAc, MeO) this ratio is approximately 25 : 75. When the substituent is Me or Cl (next paper) the ratio is *ca.* 50 : 50. The ratios are independent of the cyclising agent.

Cyclisation of a 3′-substituted 2-carboxydiphenyl ether may give a 1- or a 3-substituted xanthone according to whether ring closure takes place on the 2′- or the 6′-position.

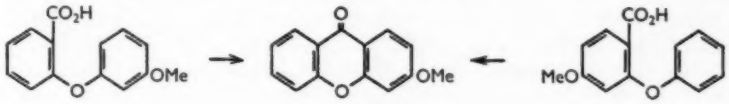
Former work [1] has shown that when R is NO_2 ($-I$, $-M$) the principal product is the 1-substituted xanthone (II), but that when R is NHAc ($-I$, $+M$) it is the isomer (III). The present communication relates to the cyclisation of acids of type (I) in which R is OMe, Me, CO_2H, CN, NO_2, or NHAc; the following paper refers to cases in which R is Cl.



(II) (I) (III)

It was of interest to examine the effect of variations of the electronic nature of R on the ratio of the two products formed by ring closure on to the 2′- and the 6′-position and also to determine whether the cyclising agent affects this ratio.

The cyclisation of acids of type (I) is an intramolecular acylation and appears to comprise two steps. The first is the rapid reversible acid-catalysed formation of a carbonium



(IV)

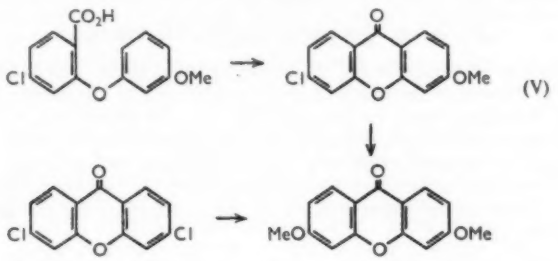
ion $-C^+=O$ and the second, the rate-determining step, involves electrophilic attack of the carbonium ion on the non-carboxylated ring. The direction of cyclisation will therefore be controlled by the relative electron-densities at positions 2′ and 6′ in the excited structures. Cyclisation of 2-carboxydiphenyl ether by polyphosphoric acid has been shown to obey first-order kinetics with 10^4k equal to 3·2 and 18·7 at 63° and 83° respectively. From these values the Arrhenius and Eyring equations give the energy of activation E^* 20,900 cal. mole^{-1} and the entropy of activation ΔS^* −13 cal. deg.$^{-1}$. The comparatively large ΔS^* apparently reflects the loss in rotational freedom about the oxygen bridge when the rigid tricyclic transition structure is formed.

Cyclisation of 2-carboxy-3′-methoxydiphenyl ether with polyphosphoric acid gave 3-methoxyxanthone (IV) in high yield, identified by reference to unequivocal material obtained by ring closure of 2-carboxy-5-methoxydiphenyl ether. Similarly, cyclisation of 2-carboxy-5-chloro-3′-methoxydiphenyl ether gave a high yield of 3-chloro-6-methoxyxanthone (V), converted by sodium methoxide into 3 : 6-dimethoxyxanthone. The orientation of the latter was proved by its identity with 3 : 6-dimethoxyxanthone obtained from authentic 3 : 6-dichloroxanthone (see below).

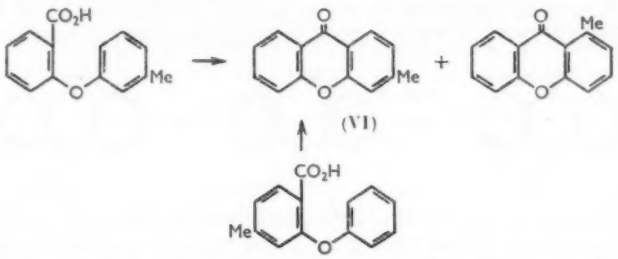
[1] Goldberg and Walker, *J.*, 1953, 1348.

XUM

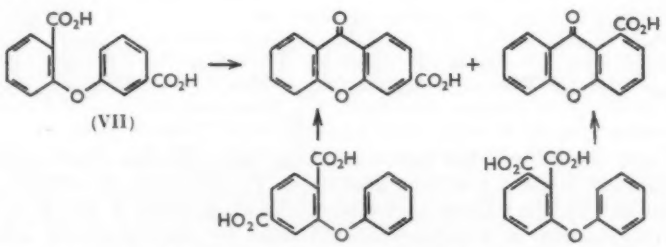
2-Carboxy-3′-methyldiphenyl ether cyclised in refluxing acetic anhydride to a mixture of two methylxanthones. These were separated by fractional crystallisation into the



less soluble 3-methylxanthone (VI), identified by reference to an unequivocal specimen obtained by cyclodehydration of 2-carboxy-5-methyldiphenyl ether, and the more soluble isomer which must be 1-methylxanthone. From the amounts of the pure isomers isolated



it was apparent that both isomers are formed in substantial quantity with a slight predominance of the 3-isomer.



Cyclisation of 2 : 3′-dicarboxydiphenyl ether (VII) with polyphosphoric acid gave a mixture of xanthonecarboxylic acids separable, by virtue of the large difference in solubilities of their pyridine salts, into xanthone-1- and -3-carboxylic acid in the ratio of 85 : 15. The orientation of the former was proved by its identity with xanthone-1-carboxylic acid obtained by condensation of 3-chlorophthalic acid with phenol and cyclisation of the resulting 2 : 3-dicarboxydiphenyl ether; the constitution of the other isomer was proved by reference to unequivocal material obtained by condensation of 2-chloro-4-methylbenzoic acid with phenol, and oxidation of the product to 2 : 5-dicarboxydiphenyl ether, followed by cyclisation. Separation of xanthone-1- and -3-carboxylic acid, *via* their pyridine salts, has been shown to be quantitatively reliable, within 1%, by application to synthetic mixtures of the pure isomers. Anschütz, Stoltenhoff, and Voeller [2] cyclised 2 : 3′-dicarboxydiphenyl ether by treatment of its diacid dichloride in tetrachloroethane

[2] Anschütz, Stoltenhoff, and Voeller, *Ber.*, 1925, **58**, 1736.

with anhydrous oxalic acid, obtaining a small yield of an acid stated to be either xanthone-1- or -3-carboxylic acid. Repetition of their work gave an 87% yield of crude product, separable by the pyridine method into xanthone-1- (77%) and -3-carboxylic acid (9%). Anschütz *et al.* apparently failed to find the principal product, the 1-carboxylic acid, because of its high solubility in the cyclising solvent. The formation of the 1- and the 3-carboxylic acid in substantially the same ratio whether polyphosphoric acid or oxalic acid (respectively a powerful and a feeble protonising agent) is used strongly supports the theoretical deduction that the cyclising agent does not affect the direction of ring closure.

m-Cyanophenol condensed with *o*-chlorobenzoic acid to yield 2-carboxy-3'-cyanodiphenyl ether; this cyclised on treatment with phosphoryl chloride to 1-cyanoxanthone, oriented by hydrolysis to xanthone-1-carboxylic acid.

Goldberg and Walker [1] cyclised 2-carboxy-3'-nitrodiphenyl ether, and also the 4-, 5-, and 6-nitro-derivative, with phosphoryl chloride or sulphuric acid, and obtained in each case *ca.* 80% yields of the product obtained by ring closure on the 2'-position, with, in some instances, a small amount (*ca.* 5—15%) of the isomer formed by cyclisation on to the 6'-position. In the present investigation the ratio of the isomers formed by cyclisation of 2-carboxy-3'-nitrodiphenyl ether has been determined with greater precision by using two novel methods of analysis. In one method the mixture was reduced and the mixed aminoxanthones were diazotised and converted into a mixture of 1- and 3-hydroxyxanthones, easily separable by virtue of the complete insolubility of the sodium salt of the former, and the comparatively large solubility of the sodium salt of the latter, in dilute sodium hydroxide. The results showed that the crude cyclisation product contained not less than 11% of 3-nitroxanthone. In the second method, the mixture of 1- and 3-aminoxanthone was photometrically analysed; 1-aminoxanthone is intensely yellow while 3-aminoxanthone is colourless. This method proved that the cyclisation product obtained with sulphuric acid at 100° contained 82% of 1- and 18% of 3-nitroxanthone.

By the same analytical procedure it has been shown that ring closure of 3'-acetamido-2-carboxydiphenyl ether with polyphosphoric acid at 100° gives a product containing 72% of 3- and 28% of 1-aminoxanthone.

The cyclodehydration of 2-carboxy-3'-nitrodiphenyl ether by polyphosphoric acid has been examined in more detail; with this reagent there is no loss by formation of water-soluble compounds (as with sulphuric acid) and the method lends itself to kinetic studies. Reduction of the mixture of 1- and 3-nitroxanthone and analysis of the product by the photometric method enabled the rate constants k_1 and k_3 (ring closure to give 1- and 3-nitroxanthone respectively) to be separated and the energies and entropies of activation calculated for the two simultaneous reactions. The energies of activation for cyclisation on to the 2'- and the 6'-position are equal within the experimental error, being *ca.* 16,000 cal. mole^{-1} above that for the cyclodehydration of 2-carboxydiphenyl ether. The ratio of the products formed by cyclisation on to the 2'- and the 6'-position is therefore independent of the activation energies but is governed entirely by the ratio of the frequency factors $A_1/A_2 = ca.\ 4{\cdot}0$.

It is apparent that for 3'-substituents having a strong $-I$, $-M$ effect (NO_2, CO_2H, CN) the ratio of products respectively formed by cyclisation on to the 2'- and the 6'-position (the 2' : 6'-closure ratio) is of the order of 80 : 20. For substituents with a strong $-I$, $+M$ effect (NHAc, MeO) this ratio is approximately 25 : 75. When the substituent is Me or Cl (next paper), the ratio is *ca.* 50 : 50. The ratio of the two isomers formed is independent of the cyclising agent.

Experimental

General Procedure for the Condensation of o-*Chlorobenzoic Acids with Phenols.*—The method previously described [1] using nitrobenzene, hexyl alcohol, or anisole as diluent was used whenever possible since this procedure can be scaled up without loss of yield. A number of such reactions, however, give meagre yields but excellent yields are obtainable by the "dry"

method originally employed by Ullmann and his collaborators. The *o*-chlorobenzoic acid, phenol, and catalyst were added in this order to hot methanol containing 3 mols. of sodium methoxide; the methanol was distilled off, the glutinous residue heated for a short time at 180—200°, and the product isolated by the usual procedure. Unfortunately this method does not give good yields when scaled up. Molecular weights of acids were determined by titration.

2-Carboxy-3′-methoxydiphenyl Ether.—*o*-Chlorobenzoic acid (15·7 g.), potassium carbonate (34 g.), *m*-methoxyphenol (16·5 g.), copper bronze (0·2 g.), cuprous iodide (0·2 g.), and nitrobenzene (100 c.c.) were stirred at 160° for 6 hr. The purified *product* separated from dilute methanol in colourless needles (10 g.), m. p. 128—130° (Found: *M*, 240. $C_{14}H_{12}O_4$ requires *M*, 244).

3-Methoxyxanthone.—The foregoing acid (7·0 g.) was heated on the water-bath with acetic anhydride (70 c.c.) and sulphuric acid (0·7 c.c.) for 1½ hr., then poured into ice-water. The precipitate was collected, extracted with N-sodium carbonate, and washed; crystallisation from 95% alcohol gave 3-methoxyanthone (4·5 g., 70%), m. p. 130—132° alone and in admixture with authentic material obtained by cyclisation of 2-carboxy-5-methoxydiphenyl ether [3] (Found: C, 73·4; H, 4·4. Calc. for $C_{14}H_{10}O_3$: C, 74·3; H, 4·4%).

3-Chloro-6-methoxyxanthone.—2 : 4-Dichlorobenzoic acid (19·1 g., 0·1 mole), *m*-methoxyphenol (18·6 g., 0·15 mole), copper bronze (0·1 g.), and cuprous iodide (0·1 g.) were added to a solution from sodium (4·6 g.; 0·2 g.-atom) in methanol (80 c.c.). The methanol was distilled off on the water-bath, nitrobenzene (10 c.c.) added, and the mixture placed in an oil-bath at 120° the temperature of which was raised during 10 min. to 190—200° and held thereat for 10 min. The product was a dark solid acid (16·1 g.) which could not be effectively purified. The crude acid was cyclised on the water-bath for 2 hr. with acetic anhydride (150 c.c.) containing sulphuric acid (0·5 c.c.), and then poured on ice. Recrystallisation from aqueous pyridine gave *3-chloro-6-methoxyxanthone* as colourless needles (8·7 g., 33% overall), m. p. 166° (Found: Cl, 13·3. $C_{14}H_9O_3Cl$ requires Cl, 13·6%).

3 : 6-Dimethoxyxanthone.—The foregoing compound (2·0 g.) was refluxed for 100 hr. with a solution from sodium (2·0 g.) in methanol (100 c.c.) and dioxan (50 c.c.). The methanol was evaporated and the residue washed with dilute hydrochloric acid and then water; recrystallisation from alcohol gave *3 : 6-dimethoxyxanthone* (1·9 g., 97%), m. p. 184—186° alone and in admixture with material obtained from 3 : 6-dichloroxanthone [4] (Found: C, 70·1; H, 4·5. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%).

Cyclisation of 2-Carboxy-3′-methyldiphenyl Ether. 1- and 3-Methylxanthone.—*o*-Chlorobenzoic acid (62·6 g.), *m*-cresol (87 g.), potassium carbonate (56 g.), nitrobenzene (300 c.c.), copper bronze (0·2 g.), and cuprous iodide (0·2 g.) were stirred at 160—165° for 5 hr. 2-Carboxy-3′-methyldiphenyl ether crystallised from aqueous alcohol as colourless needles (42 g.), m. p. 95° (Found: *M*, 229. Calc. for $C_{14}H_{12}O_3$: *M*, 228).

A solution of this acid (10 g.) in acetic anhydride (100 c.c.) and sulphuric acid (2 c.c.) was refluxed for 1½ hr., then poured on ice. The precipitate was collected, extracted with aqueous sodium carbonate, washed, and dried. The mixture of 1- and 3-methylxanthone (8·6 g.; m. p. 70—80°) was crystallised six times from 85% methanol, to give *1-methylxanthone* (1·6 g.) as long colourless needles, m. p. 114°, which strongly depressed the m. p. of authentic 3-methylxanthone (m. p. 92°) obtained by cyclisation of 2-carboxy-5-methyldiphenyl ether (Found: C, 80·2; H, 4·6. $C_{14}H_{10}O_2$ requires C, 80·1; H, 4·8%).

The mother-liquors from the first, second, and third crystallisations above, when kept for 7 days, deposited needles, m. p. 65—75°. These were combined and crystallised six times from dilute methanol to give *3-methylxanthone* (1·2 g.), m. p. 94°, depressed in admixture with 1-methylxanthone but not with authentic 3-methylxanthone (Found: C, 80·0; H, 4·7. $C_{14}H_{10}O_2$ requires C, 80·1; H, 4·8%).

2-Carboxy-3′-methyldiphenyl ether was not cyclised by acetic anhydride at 100° in 1 hr.

Cyclisation of 2 : 3′-Dicarboxydiphenyl Ether.—(i) *With polyphosphoric acid.* A mixture of 2 : 3′-dicarboxydiphenyl ether [3] (10 g.) and polyphosphoric acid (170 g.) was stirred at 100° for 80 min., kept at room temperature for a further 3 hr., then stirred with water (300 c.c.). The precipitate was collected and dissolved in excess of warm dilute sodium hydroxide solution, the solution filtered (charcoal), and the acid (8·7 g.; m. p. 218—224°) reprecipitated. The acid (8·0 g.) was dissolved in hot pyridine (20 c.c.), water (200 c.c.) was added, and the clear

[3] Ullmann and Wagner, *Annalen*, 1907, **355**, 369.
[4] Goldberg and Wragg, following paper.

XUM

solution left in the refrigerator for 10 days. The crystalline precipitate was collected, drained, and washed into the filtrate (*A*) with a little water, then boiled with water (200 c.c.) and 5N-sodium hydroxide (5 c.c.). The salt dissolved and the pyridine passed off in the steam. Acidification yielded *xanthone-3-carboxylic acid* (0·8 g., 10%), m. p. 304—306°. Crystallisation from alcohol–dioxan gave the pure compound as needles, m. p. 320° alone and in admixture with authentic material obtained by cyclisation of 2 : 5-dicarboxydiphenyl ether (Found; *M*, 241. $C_{14}H_8O_4$ requires *M*, 240).

The pyridine filtrate (*A*) was heated to 70°, excess of hydrochloric acid added, and the precipitate of xanthone-1-carboxylic acid (7·0 g., 88%; m. p. 230°) collected; crystallisation from alcohol–dioxan gave the pure acid, m. p. 232° alone and in admixture with authentic material obtained by cyclisation of 2 : 3-dicarboxydiphenyl ether but depressed in admixture with xanthone-3-carboxylic acid (Found: *M*, 242).

When an artificial mixture of pure xanthone-1- (3·5 g.; m. p. 320°) and -3-carboxylic acid (0·4 g.; m. p. 232°) was separated by the above procedure there were obtained 0·39 g. of the 3-carboxylic acid, m. p. 316—318°, and 3·49 g. of the 1-carboxylic acid, m. p. 226—228°.

(ii) *Cyclisation of the diacid dichloride with oxalic acid* (cf. Anschütz [2] *et al.*). 2 : 3'-Dicarboxydiphenyl ether (2·58 g., 0·01 mole) was suspended in cold tetrachloroethane (60 c.c.); phosphorus pentachloride (5·0 g., 0·024 mole) was added, and the mixture heated at 100° for ½ hr. and set aside overnight. The volatile materials were pumped off at 100° and the residual oil was redissolved in tetrachloroethane (60 c.c.). Anhydrous oxalic acid (1·8 g., 0·02 mole) was added, and the temperature raised during 10 min. to the b. p. and kept thereat for a further 10 min. The solvent was evaporated and the residue dissolved in water (60 c.c.) containing excess of sodium carbonate; the solution was extracted with chloroform (2 × 25 c.c.), the filtered (charcoal) aqueous layer adjusted to pH 1, and the precipitate (2·0 g., 84%; m. p. 214—220°) collected (Found: *M*, 236). Separation through the pyridine salts yielded 0·17 g. (9%) of xanthone-3-carboxylic acid, m. p. 316°, and 1·54 g. (78%) of xanthone-1-carboxylic acid, m. p. 228°.

1·0 g. of xanthone-1-carboxylic acid just dissolves in 4·5 c.c. of boiling tetrachloroethane and in 95 c.c. at room temperature; 1·0 g. of xanthone-3-carboxylic acid in 500 c.c. of boiling tetrachloroethane; 1·0 g. of 2 : 3'-dicarboxydiphenyl ether in 50 c.c. of tetrachloroethane at the b. p.

2 : 3-*Dicarboxydiphenyl Ether*.—3-Chlorophthalic acid (30·1 g.), phenol (70·5 g.), potassium carbonate (52 g.), nitrobenzene (250 c.c.), copper bronze (0·5 g.), and cuprous iodide (0·5 g.) were stirred at 165—170° for 6 hr. The product (17 g.) was dissolved in N-sodium carbonate (200 c.c.), potassium permanganate (10 g.) slowly added, and the solution boiled for ½ hr.: sodium metabisulphite (30 g.) was added and the *dicarboxylicacid* (14·6 g.; m. p. 202°) precipitated. It crystallised from dilute ethanol as colourless needles, m. p. 204° (Found: *M*, 132; C, 65·1; H, 3·9%. $C_{14}H_{10}O_5$ requires *M*, 129; C, 65·1; H, 3·9%).

Xanthone-1-carboxylic Acid (cf. below).—A mixture of the foregoing acid (5 g.) and polyphosphoric acid (95 g.) was stirred at 100° for 4 hr., then kept at room temperature for 2 days. Water (150 c.c.) was added, the precipitate collected and dissolved in diluted aqueous sodium hydroxide, and the filtered solution acidified. Crystallisation from alcohol–dioxan gave *xanthone-1-carboxylic acid* (3·1 g.), m. p. 231—232° (Found: C, 69·9; H, 3·3. $C_{14}H_8O_4$ requires C, 70·0; H, 3·3%).

2-*Carboxy-5-methyldiphenyl Ether*.—4-Amino-3-chlorotoluene (35·4 g.) in 10N-hydrochloric acid (50 c.c.) and water (200 c.c.) was diazotised at 2° by sodium nitrite (17·25 g.) in water (50 c.c.). After a further 15 min. the solution was added during 10 min. to a vigorously refluxing solution of nickel chloride hexahydrate (63 g.) and sodium cyanide (63 g.) in water (400 c.c.). The mixture was boiled for a further 30 min., then distilled in steam; 3-chloro-4-cyanotoluene (27 g., 70%) distilled and formed a white solid, m. p. 60—62°. This compound (15·2 g.) was refluxed with sodium hydroxide (30 g.) and water (70 c.c.) for 9 hr. In the morning the solution was reheated, then filtered (charcoal), and the 2-chloro-4-methylbenzoic acid (15·7 g.; m. p. 156°) precipitated by acidification.

This acid (25·6 g.), phenol (85 g.), potassium carbonate (52 g.), nitrobenzene (250 c.c.), copper bronze (0·5 g.), and cuprous iodide (0·5 g.) were stirred at 160—165° for 6 hr. *2-Carboxy-5-methyldiphenyl ether* was isolated as colourless prisms (12·7 g.; from dilute methanol), m. p. 132—133° (Found: *M*, 229. $C_{14}H_{12}O_2$ requires *M*, 228).

2 : 5-*Dicarboxydiphenyl Ether*.—Potassium permanganate (55 g.) was added portionwise

XUM

during ½ hr. to a boiling solution of the foregoing acid (10 g.) in N-sodium carbonate (550 c.c.). The mixture was refluxed for a further ½ hr., then sodium pyrobisulphite (60 g.) was added and the stirred mixture strongly acidified with hydrochloric acid. The precipitate was collected and purified by dissolution in aqueous sodium carbonate, filtration (charcoal), and reprecipitation. The *acid* crystallised from aqueous ethanol as colourless needles (7·0 g.), m. p. 300° (Found: C, 65·0; H, 4·0. $C_{14}H_{10}O_5$ requires C, 65·1; H, 3·9%).

Xanthone-3-carboxylic Acid.—The foregoing acid (2·58 g.) was heated with polyphosphoric acid (37 g.) at 100° for 1½ hr. The crude product (2·3 g.; m. p. 264°) on crystallisation from alcohol–dioxan yielded *xanthone-3-carboxylic acid* (1·5 g.) as colourless needles, m. p. 308° (Found: C, 69·8; H, 3·4. $C_{14}H_8O_4$ requires C, 70·0; H, 3·3%).

3-*Methylxanthone.*—A solution of 2-carboxy-5-methyldiphenyl ether (4·5 g.) in acetic anhydride (40 c.c.) and sulphuric acid (0·5 c.c.) was heated on the water-bath for 1½ hr., then kept at room temperature overnight. The solution was stirred with ice-water (300 g.) and set aside. The precipitate, after extraction with hot aqueous sodium carbonate, crystallised from aqueous methanol to give 3-methylxanthone (3·2 g.) as needles, m. p. 97° (Found: C, 79·9; H, 4·9. Calc. for $C_{14}H_{10}O_2$: C, 80·1; H, 4·8%).

m-*Cyanophenol.*—The following is the route used by Culbertson, Carpenter, and Nielsen [5] who did not give experimental details. *m*-Hydroxybenzaldehyde (48·8 g.) was added during 15 min. to a solution of hydroxylamine hydrochloride (28 g.) in water (60 c.c.) and 5N-sodium hydroxide (80 c.c.) stirred at room temperature, and the solution was then heated on the water-bath for 15 min. and set aside. In the morning the precipitated oil was separated and the aqueous layer saturated with ammonium sulphate and extracted with ether (4 × 100 c.c.). The oil and ether extracts were combined and dried (Na_2SO_4), and the ether distilled off. The residual oily oxime was dried at 100°/10 mm., refluxed with acetic anhydride (120 c.c.) for 3 hr., and poured on crushed ice (500 g.), and the mixture was rapidly stirred at 0—10° for 2 hr. in order to free the precipitated oil from occluded acetic anhydride. The oil was collected and refluxed with 2·5N-sodium hydroxide (400 c.c.) for 45 min., and the solution filtered (charcoal), acidified with 10N-hydrochloric acid (90 c.c.), and extracted with ether (4 × 300 c.c.). The ether extracts were dried (Na_2SO_4), the ether was distilled off, and the oil dissolved in chloroform (250 c.c.) and carbon tetrachloride (100 c.c.). Distillation of *ca.* 200 c.c. of the solvent and then addition of ligroin to the residue precipitated pale ochre *m*-cyanophenol (25 g.), m. p. 80—85°.

2-*Carboxy-3′-cyanodiphenyl Ether.*—*o*-Chlorobenzoic acid (7·83 g., 0·05 mole), *m*-cyanophenol (6·6 g., 0·055 mole), and a trace of copper–copper iodide catalyst were added to a solution from sodium (2·3 g., 0·1 g.-atom) in methanol (50 c.c.). The methanol was distilled off at 10 mm. and the residual solid placed in an oil-bath at 120° and the temperature raised to 180° during 10 min. Boiling nitrobenzene (10 c.c.) was added with mixing and the heating continued for a further 20 min. Water (150 c.c.) and potassium carbonate (5 g.) were added, the nitrobenzene removed by extraction with ether, and the aqueous layer acidified. The precipitate was collected and dissolved in aqueous potassium carbonate, the solution filtered (charcoal), and the *acid* (10 g.) reprecipitated. Crystallisation from dilute methanol gave the pure acid (5 g.), as colourless prisms m. p. 148—150° (Found: *M*, 238; C, 70·6; H, 3·8; N, 6·0%. $C_{14}H_9O_3N$ requires *M*, 239; C, 70·3; H, 3·8; N, 5·9%).

1-*Cyanoxanthone.*—The foregoing acid (3 g.) was refluxed with phosphoryl chloride (25 c.c.) for 3 hr. and the solution poured on ice (200 g.). The precipitate was collected and extracted with hot aqueous potassium carbonate; crystallisation twice from aqueous dioxan gave 1-*cyanoxanthone* (1·4 g.) as fawn needles, m. p. 196—198° (Found: C, 76·7; H, 3·1; N, 6·2. $C_{14}H_7O_2N$ requires C, 76·1; H, 3·2; N, 6·3%).

Xanthone-1-carboxylic Acid (cf. above).—A solution of the cyano-compound (1 g.) in dioxan (20 c.c.) and 6N-sodium hydroxide (40 c.c.) was heated on the water-bath for 80 hr. The solvent was evaporated, water added, the insoluble material removed, the filtered solution acidified, and the precipitate crystallised from alcohol–dioxan–water. Xanthone-1-carboxylic acid (0·4 g.) was obtained in prisms, m. p. 230—232° alone and in admixture with a sample obtained from 3-chlorophthalic acid (Found: *M*, 238. Calc. for $C_{14}H_8O_4$: *M*, 240).

Cyclisation of 2-Carboxy-3′-nitrodiphenyl Ether.—The acid was cyclised with sulphuric acid by the method of Goldberg and Walker.[1] The *crude* product (25 g.; m. p. 182—192°) was crystallised five times from 90% pyridine to yield 13·2 g. of pure 1-nitroxanthone, m. p. 202°;

[5] Culbertson, Carpenter, and Nielsen, *Proc. Iowa Acad. Sci.*, 1930, **37**, 248.

evaporation of the mother-liquors gave 9·5 g. of a mixture of 1- and 3-nitroxanthone. The latter (9·5 g.) was reduced with stannous chloride (60 g.) and 10N-hydrochloric acid (60 c.c.) by the method previously described, and the mixture of 1- and 3-aminoxanthone (8·2 g.) isolated. This was dissolved in sulphuric acid (25 c.c.), and the solution poured into water (130 c.c.) with vigorous stirring. The fine suspension was diazotised at 2° with sodium nitrite (2·9 g.) in water (12 c.c.) and, after 15 minutes' stirring at room temperature, added dropwise to a boiling solution of copper sulphate pentahydrate (18 g.) in 5N-sulphuric acid (650 c.c.). After boiling for a further 10 min. the mixture was cooled, the insoluble material collected and ground with excess of 5N-sodium hydroxide and the mixture filtered. The insoluble portion was extracted again in the same manner. Acidification of the combined extracts gave 3-hydroxyxanthone (2·5 g.), m. p. and mixed m. p. 240—242°. The insoluble sodium salt of the 1-hydroxyxanthone was ground in a ball-mill with 5N-sulphuric acid, and the mixture extracted in the ball-mill with ether (5 × 25 c.c.). Evaporation of the ether gave crude 1-hydroxyxanthone (1·86 g.); distillation of this in steam gave the pure compound (1·1 g.), m. p. 148°. The isolation of 2·5 g. of 3-hydroxyxanthone indicated that the original crude product of cyclisation of 2-carboxy-3'-nitrodiphenyl ether contained not less than 11% of 3-nitroxanthone.

Photometric Analysis of Mixtures of 1- *and* 3-*Aminoxanthone.*—The optical density of a 0·02% solution of 1-aminoxanthone in methanol in a 2 cm. cell in a Spekker Photometer with the No. 7 Purple Chance glass filter [6] (transmitting principally in the 4000—4700 Å range) was 0·58 (ε 306); that of a similar solution of 3-aminoxanthone was 0·015 (ε 7·95). For synthetic mixtures of the pure isomerides containing a *total* of 0·02% of aminoxanthones (with % 1-aminoxanthone in parentheses) the optical densities were 0·015 (0); 0·18 (10); 0·275 (20); 0·340 (30); 0·390 (40); 0·44 (50); 0·48 (60); 0·51 (70); 0·53 (80); 0·56 (90); 0·58 (100). From the plot it was possible to analyse unknown mixtures with an estimated precision of ±1%.

Experiments on Reaction Kinetics.—Polyphosphoric acid was prepared by the portionwise addition of phosphoric oxide (186 g.) to 90% orthophosphoric acid (d = 1·75; 120 c.c.) with hand-swirling. The temperature rose steeply. After ½ hr. the mixture was heated on the water-bath for 2 hr. with occasional shaking. The product was a colourless viscous liquid which slowly solidified; it was used within 6 weeks of preparation.

(i) *Cyclisation of* 2-*carboxydiphenyl ether.* Polyphosphoric acid (50 g.) was stirred in a thermostat until temperature equilibrium was attained, and the 2-carboxydiphenyl ether (5·0 g.) then added. After a given time interval the flask was removed, ice-water (400 c.c.) quickly added, and the whole set aside for 2 hr. The precipitate was collected, washed with water, extracted with boiling 10% aqueous sodium carbonate (200 c.c.) to remove uncyclised carboxylic acid, again washed, dried, and weighed. Acidification of the alkali extract gave unchanged starting acid; the amount of unrecovered material was usually 0·1—0·2 g. The first-order reaction equation $kt = \ln [a/(a - x)]$, where a was the initial concentration of 2-carboxydiphenyl ether and x the concentration of xanthone at time t, gave 10^4k, for reaction times 15, 30, 50, and 80 min., at 63°, respectively, 3·4, 3·4, 3·1, and 2·9 (average 3·2). At 83° the values of 10^4k, for reaction times 10, 10, 15, and 20 min., were 20·7, 19·1, 16·4, and 18·7 (average 18·7). By using the Arrhenius and Eyring equations $k = A \exp - E^*/RT$ and $k = (RT/Nh) \exp(-E^*/RT) . \exp(\Delta S^*/R)$ where R = 1·987 cal. deg.$^{-1}$, R/N (Boltzmann constant) = 1·3805 × 10^{-16} erg deg.$^{-1}$, h (Planck constant) = 6·624 × 10^{-27} erg sec., these values for the k's give E^* = 20,900 cals. mole^{-1}; log A = 10·1; and ΔS^* = −13 cals. deg.$^{-1}$.

(ii) *Cyclisation of* 2-*carboxy*-3'-*nitrodiphenyl ether.* The values found by the same method for $10^4(k_1 + k_3)$, where k_1 is the reaction rate for cyclisation to 1-nitroxanthone and k_3 that for cyclisation to 3-nitroxanthone at 63° (with reaction time in min. in parentheses) were 0·15 (70), 0·16 (90), 0·19 (150), 0·17 (210), and 0·14 (300) with an average of 0·16. At 83° the values for $10^4(k_1 + k_3)$ were 3·46 (8), 3·74 (15), 3·68 (22), and 3·36 (30) with an average value of 3·56.

In order to obtain separate values for k_1 and k_3 it was necessary to determine the ratio of 1- and 3-nitroxanthone formed at each reaction temperature. The mixture of nitroxanthones (5·0 g.), stannous chloride dihydrate (40 g.), and 10N-hydrochloric acid (40 c.c.) was stirred on the water-bath for 2½ hr. In the morning the mass was stirred with 5N-sodium hydroxide (250 c.c.) and ice (250 g.) for 2 hr., and the solid collected and ground with cold N-sodium hydroxide (150 c.c.) in a glass ball-mill to remove traces of tin. The yellow solid was collected washed, and dried at 40°/10 mm.; the recovery was ~ 95%. The mixture obtained from each

[6] Delory, "Photoelectric Methods in Clinical Biochemistry," Hilger and Watts, 1949, p. 19.

XUM

series was analysed photometrically. For the cyclisations at 63° the optical density of the standard 0·02% solution was 0·524 (76% of 1- and 24% of 3-aminoxanthone); for the cyclisation at 83° the optical density was 0·518 (74% of 1- and 26% of 3-aminoxanthone). Accordingly, at 63°, $10^4k_1 = 0{\cdot}12$, and $10^4k_3 = 0{\cdot}04$; and at 83°, $10^4k_1 = 2{\cdot}68$, and $10^4k_3 = 0{\cdot}88$. These values give for ring closure on to the 2′-position to yield 1-nitroxanthone: $E^*_1 = 36{,}920$ cal. mole^{-1}, log $A_1 = 19{\cdot}1$, $\Delta S^*_1 = 29$ cal. deg.$^{-1}$; and for simultaneous ring closure on to the 6′-position to give 3-nitroxanthone, $E^*_3 = 36{,}740$ cal. mole^{-1}, log $A_3 = 18{\cdot}5$, $\Delta S^*_3 = 26$ cal. deg.$^{-1}$.

Cyclisation of 3-Acetamido-2′-carboxydiphenyl Ether.—Acetic anhydride (20 g.) was added during 45 min. to a solution of the 3′-amino-2-carboxylic acid [1] (11 g.) in sodium carbonate (23 g.) and water (200 c.c.) stirred at 15°. After a further 15 minutes' stirring the mixture was adjusted to pH 8·5, filtered (charcoal), and acidified. The precipitated *acetamido-acid* (11·5 g., m. p. 196°) crystallised from aqueous-alcoholic dioxan in prisms, m. p. 198—200° (Found: N, 5·2. $C_{15}H_{13}O_4N$ requires N, 5·2%).

(i) The acetamido-acid (5 g.) was heated for 2 hr. at 100° with polyphosphoric acid (50 g.); water (20 c.c.) was added, heating continued for 1 hr., and the solution poured on ice. In the morning the precipitate (3·2 g.; m. p. 190—210°) was collected, washed, and dried. A 0·02% solution in methanol in a 2 cm.cell had an optical density of 0·328 (No. 7 light filter); this indicated a composition of 72% of 3- and 28% of 1-aminoxanthone.

(ii) The acetamido-acid (5 g.) was heated at 100° with acetic anhydride (15 c.c.) and sulphuric acid (10 c.c.) for ½ hr., the solution poured into ice water, and the precipitate collected and extracted with dilute sodium carbonate. Crystallisation from aqueous pyridine gave 3-acetamidoxanthone (2·0 g.) as buff plates, m. p. 312° (Found: N, 5·6. Calc. for $C_{15}H_{11}O_3N$: N, 5·5%): hydrolysis with 75% sulphuric acid at 100° for 1 hour yielded 3-aminoxanthone, m. p. 234—235°.

The authors thank Mr. R. J. Crabbe for technical assistance.

RESEARCH DEPARTMENT, WARD, BLENKINSOP & CO., LTD.,
ANGLO ESTATE, SHEPTON MALLET, SOMERSET. [*Received, June 5th*, 1958.]

---

860. *Reactivity of Xanthones bearing 1- and 3-Chloro-substituents towards Nucleophilic Reagents.*

By A. A. GOLDBERG and A. H. WRAGG.

1-Chloroxanthones with toluene-*p*-sulphonamide give high yields of 1-toluene-*p*-sulphonamidoxanthones: 3-chloroxanthones do not react. The reaction has been employed to determine the ratio of products formed by cyclisation on to the 2′- and the 6′-position in 2-carboxy-3′-chloro- and 2-carboxy-3′ : 5-dichloro-diphenyl ether. In both cases this ratio is *ca.* 1·0 and is independent of the cyclising agent.

Both 1- and 3-chloroxanthone react quantitatively with sodium methoxide to yield the methoxyxanthone. The method constitutes a novel and easy route to 3-alkoxy-, 3-aryloxy-, and 3-arylthio-xanthones.

1-CHLOROXANTHONE was required for chemotherapeutic studies and various synthetic routes to the compound have been explored. Dhar [1] cyclised 2-carboxy-3′-chlorodiphenyl ether with sulphuric acid and obtained a monochloroxanthone, m. p. 100°, which he believed to be the (then) unknown 1-chloroxanthone. Repetition of Dhar's work, using acetic anhydride as cyclising agent, gave a compound of the same m. p. but this was not 1-chloroxanthone because the latter, obtained by the Sandmeyer reaction from 1-aminoxanthone, had m. p. 137°. Exhaustive fractional crystallisation and chromotography failed to raise the m. p. of Dhar's compound which evidently contained much 3-chloroxanthone since synthetic mixtures of 1- and 3-chloroxanthone (m. p. 137° and 130° respectively) all had m. p. 100—102° provided not less than 25% of either isomer was present.

[1] Dhar, *J.*, 1920, 1061.

Comparison of the ultraviolet spectrum of Dhar's compound with those of pure 1- and 3-chloroxanthone indicated the presence of 40—60% of 3-chloroxanthone but the spectra of the pure isomers were too similar to allow of greater precision. Accordingly a method of analysis and possible separation was sought making use of an expected difference between the reactivity of xanthone at the 1- and the 3-position with nucleophilic reagents. Reactivity at the 1-position is known to be considerable with both amines [2] and alkoxide ions.[3]

It was found that 1-chloroxanthone reacted with toluene-*p*-sulphonamide in refluxing pentyl alcohol, in the presence of potassium carbonate and a copper catalyst, to give 1-toluene-*p*-sulphonamidoxanthone with release of 74% of the theoretical amount of halide ion in 6 hours; under the same conditions 3-chloroxanthone did not react. Determination of the halide ion released when Dhar's compound was submitted to this procedure showed that it consisted of 56% of 1-chloroxanthone and 44% of 3-chloroxanthone. Since the sulphonamide is far less soluble than either of the monochloroxanthones it can be separated almost quantitatively; hydrolysis affords a new route to 1-aminoxanthone.

With the more reactive nucleophile, methoxide ion in refluxing methyl alcohol, both 1- and 3-chloroxanthone reacted quantitatively to give the corresponding methoxyxanthone. With Dhar's compound, the mixture of the 1- and 3-methoxyxanthone thus obtained, upon fractional crystallisation, yielded 3-methoxyxanthone in *ca.* 25% overall yield; the more soluble 1-methoxyxanthone could not be isolated. It is of passing interest, since 3-chloroxanthone is readily accessible from 2 : 4-dichlorobenzoic acid, that this method constitutes a novel and easy route to 3-alkoxy-, 3-aryloxy-, and 3-aralkyloxy-xanthones.

Cyclisation of 2-carboxy-3' : 5-dichlorodiphenyl ether with sulphuric acid gave a mixture of 1 : 6- and 3 : 6-dichloroxanthone. Fractional crystallisation gave the less soluble 3 : 6-dichloroxanthone in *ca.* 20% yield, identified by reference to unequivocal material obtained from 3 : 6-diaminoxanthone [4]; 1 : 6-dichloroxanthone could not be isolated from the mixture. Treatment of the crude cyclisation mixture of 1 : 6- and 3 : 6-dichloroxanthones with toluene-*p*-sulphonamide in refluxing pentyl alcohol (134°) did not result in reaction; in a refluxing mixture of hexyl and octyl alcohol (166°), however, reaction took place with production of 6-chloro-1-toluene-*p*-sulphonamidoxanthone. The structure of this compound was ascertained by hydrolysis to an amino-chloro-xanthone, identical with the compound obtained by cyclisation of 2-carboxy-5-chloro-3'-nitrodiphenyl ether and reduction of the chloronitroxanthone thus obtained; this identity proved both to be 1-amino-6-chloroxanthone. The yield of 6-chloro-1-toluene-*p*-sulphonamidoxanthone indicated that the crude cyclisation mixture consisted of 1 : 6- and 3 : 6-dichloroxanthone in the ratio of 52 : 48. It is noteworthy that neither the cyclising agent (acetic anhydride or sulphuric acid or polyphosphoric acid) nor the 5-chloro-substituent affects the ratio of products formed by ring closure on to the 2'- and the 6'-position; this ratio appears to be a function of the 3'-chloro-substituent alone.

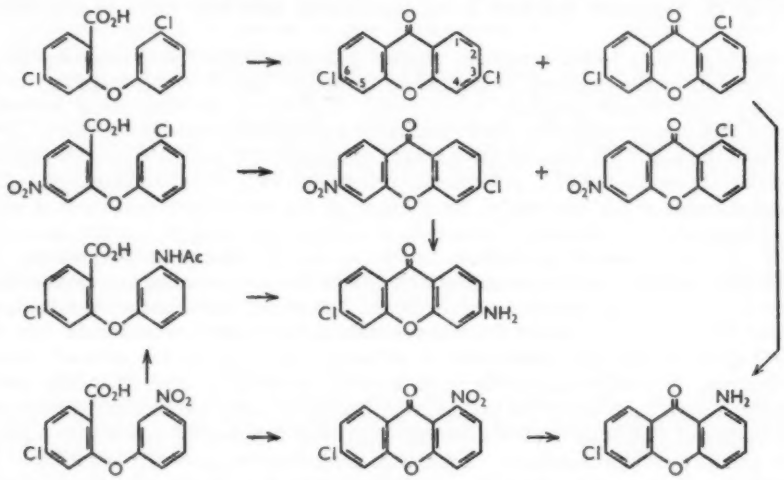
Reaction of 3 : 6-dichloroxanthone with methoxide gave 3 : 6-dimethoxyxanthone; with the crude product of cyclisation of 2-carboxy-3' : 5-dichlorodiphenyl ether, sodium methoxide gave a mixture of dimethoxyxanthones from which only 3 : 6-dimethoxyxanthone could be isolated.

Cyclisation of 2-carboxy-3'-chloro-5-nitrodiphenyl ether yielded a mixture of the less soluble 3- and the more soluble 1-chloro-6-nitroxanthone. The structure of the former was proved by reduction to 6-amino-3-chloroxanthone identical with the product obtained by cyclisation of 3'-acetamido-2-carboxy-5-chlorodiphenyl ether followed by hydrolysis.

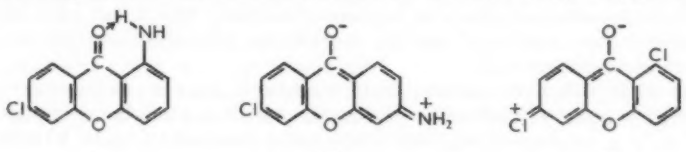
The extent of the reaction of a nucleophile at the position *para* to a carbonyl group is a function of the intensity of the polarisation or polarisability of the carbonyl group and also of the transmissibility of the $-E$ mechanism of the latter to the *para*-position. As the series α-methylbenzyl alcohol, di- and tri-phenylmethanol, 9-hydroxyxanthen is

[2] Mauss, *Chem. Ber.*, 1948, **81**, 19.
[3] Eckert and Engler, *J. prakt. Chem.*, 1922, **104**, 95.
[4] Goldberg and Walker, *J.*, 1953, 1348.

ascended there is increasing tendency for ionisation [5] (with fission of hydroxyl ion) because of increasing resonance stabilisation of the residual cation. Similarly, as the series acetophenone, benzophenone, xanthone is ascended there would be expected to be increasing polarisation of the carbonyl group (C=O) because of increasing resonance stabilisation of



the cyclic portion of the dipole. Accordingly the reactivity of 4-chloroacetophenone, 4-chlorobenzophenone, and 3-chloroxanthone towards nucleophiles should increase in this order. This has been shown to be the case; Table 1 indicates the extent of the reaction of the chloro-compound with sodium methoxide under standard conditions as measured by release of chloride ion or yield of methoxy-compound. With 3-chloroxanthones bearing a second substituent in the non-chlorinated ring, the second substituent may inhibit transmission of the $-E$ mechanism of the carbonyl group to the 3-position. Thus, while 2-amino-6-chloroxanthone reacts with methoxide ion at substantially the same speed as 3-chloroxanthone, 3-amino-6-chloroxanthone reacts extremely slowly and 1-amino-6-chloroxanthone not at all. This lack of reactivity is attributable, in the latter case, to hydrogen-bonding between the 1-amino-substituent and the carbonyl-oxygen atom (cf. I)



(I) (II) (III)

and, in the case of 3-amino-6-chloroxanthone, to the substantial weight which must be attributed to the *p*-quinonoid structure (II) in the resonance hybrid.

The smaller facility with which 1 : 6-dichloroxanthone reacts with toluene-*p*-sulphonamide than does 1-chloroxanthone reflects the statistical weighting attributable to the quinonoid structure (III).

The high reactivity of 1- and the non-reactivity of 3-chloroxanthone with toluene-*p*-sulphonamide is significant in view of the greater reactivity of methoxide ion with 3-chloroxanthone. It appears that the reaction of 1-chloroxanthone with the sulphonamide is

[5] Shriner in "Roger Adams Symposium," Chapman and Hall, London, 1954, p. 103; Goldberg and Wragg, *J.*, 1957, 4823.

TABLE 1. *Methoxydechlorination of chloro-ketones in refluxing methanol with* 10 *mols. of methoxide ion in* 72 *hours.*

Compound	Reaction (%)
4-Chloroacetophenone	27
4-Chlorobenzophenone	55
3-Chloroxanthone	100

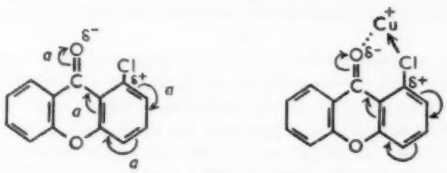
TABLE 2. *Methoxydechlorination of chloroxanthones in a refluxing mixture of* 66% *methanol and* 33% *dioxan with* 10 *mols. of methoxide ion in* 72 *hours.*

Compound	Reaction (%)	Compound	Reaction (%)
1-Chloroxanthone	~95 [a]	1-Amino-6-chloroxanthone	0
2-Chloroxanthone	0	2-Amino-6-chloroxanthone	100
3-Chloroxanthone	100 [b]	3-Amino-6-chloroxanthone	15
4-Chloroxanthone	0		

[a] 54% in 30 hours. [b] 61% in 30 hours.

mediated by two mechanisms, (*a*) the electromeric polarisation of the system C=C—C=O and (*b*) the formation of a 6-membered chelate copper complex in which the normal inductive effect of the C→Cl bond and the inductomeric polarisability of the bond in the presence of an attacking anionoid reagent will be strongly augmented by the co-ordination of the chlorine with the copper. Both these processes will operate in concert to create electron-defect at position 1, the combined total effect being sufficient to allow this position to be easily susceptible to attack by the sulphonamide with ejection of the halogen as chloride ion. The electromeric polarisation (*a*) will be fully transmitted to the 3-position but no copper chelate complex can be formed between the carbonyl-oxygen atom and a 3-halogen substituent; accordingly the net electron-defect at position 3 will be insufficient to initiate attack by the sulphonamide at this point. Formation of a chelate copper complex in the reaction of 1-chloroxanthone with toluene-*p*-sulphonamide is supported by the familiar sequence of unusual colours which accompany the reaction; these colours are frequently diagnostic of metallic inner complex salts.[6,7]

With the smaller and more vigorous nucleophile, methoxide ion, the electromeric polarisation (*a*) will create sufficient electron-defect at both positions 1 and 3 to initiate



attack at both these positions; but, because of the greater distance from the negative charge on the oxygen of the polarised carbonyl group, the approach of the methoxide ion will be less hindered at position 3 than at position 1.

It is pertinent to compare the high reactivity of the 2- and non-reactivity of the 4-halogen atom in 2 : 4-dichlorobenzoic acid towards arylamines and phenols in the presence of copper,[8] and the greater reactivity of the 4- than of the 2-halogen atom in 2 : 4-dichlorobenzoic acid towards methoxide.[9]

EXPERIMENTAL

2-Carboxy-3'-chlorodiphenyl Ether.—*o*-Chlorobenzoic acid (31·3 g., 0·2 mole), *m*-chlorophenol (28 g., 0·22 mole), potassium carbonate (35 g., 0·25 mole), and cuprous iodide (0·2 g.) were stirred with nitrobenzene (200 c.c.) at 160—165° for 6 hr. The mixture was acidified, the nitrobenzene distilled off in steam, and the residual solution strongly acidified. The black oil was collected and dissolved in diluted sodium carbonate, the solution acidified to pH 6, and the precipitated tar

[6] Morgan and Drew, *J.*, 1920, 1456.
[7] Diehl, *Chem. Rev.*, 1937, **21**, 39.
[8] Goldberg, *J.*, 1952, 4368.
[9] van der Lande, *Rec. Trav. chim.*, 1932, **51**, 98.

filtered off (charcoal); further acidification precipitated a buff oil which slowly solidified (18·5 g.; m. p. 90°). The acid was purified by dissolving it in boiling N-sodium carbonate (300 c.c.) and adding potassium permanganate (30 g.) portionwise; after 15 min. on the water-bath the mixture was cooled and acidified with dilute sulphuric acid, and the manganese oxides were removed by passing in sulphur dioxide. The residual colourless solid (13 g.; m. p. 100°) was collected and washed with water; a sample separated from aqueous alcohol in colourless leaves, m. p. 101° (Found: *M*, 252. Calc. for $C_{13}H_9O_3Cl$: *M*, 248·5).

Cyclisation of 2-*Carboxy*-3′-*chlorodiphenyl Ether*.—The acid (26 g.) was refluxed with acetic anhydride (300 c.c.) and sulphuric acid (8 drops) for 1 hr. and the solution poured on ice. The oily precipitate was extracted with hot dilute aqueous sodium carbonate and the insoluble mixture of 1- and 3-chloroxanthones (21 g.; m. p. 90—96°) (*A*) collected. Crystallisation from aqueous alcohol gave colourless plates (18 g.) (*B*), m. p. 100—102° (Found: Cl, 15·6. Calc. for $C_{13}H_7O_2Cl$: Cl, 15·4%), $\lambda_{max.}$ 2380 (ε 41,300), 2650 (ε 14,300), and 3350 Å (ε 7900), $\lambda_{min.}$ 2500 (ε 10,600), and 3050 Å (ε 1850). Comparison with the spectra of pure 1- and 3-chloroxanthone showed the mixture to contain 40—60% of 1- and 60—40% of 3-chloroxanthone.

Recrystallisation of this mixture (8 g.) twelve times gave material (3 g.) of m. p. 102—104°; the mother-liquors from the first six crystallisations were combined and evaporated, and the residue was crystallised six times to give material of the same m. p. A solution of the mixture (1·0 g.) in ethanol (15 c.c.) was chromotographed on a 30 cm. alumina column and eluted with ethanol into 7 fractions; all these had the same m. p.

Analysis of the 1- *and* 3-*chloroxanthone mixture*. The mixture of 1- and 3-chloroxanthone (2·305 g., 0·01 mole), toluene-*p*-sulphonamide (3·42 g., 0·02 mole), fused sodium acetate (1·64 g., 0·02 mole), and copper acetate (0·2 g.) was refluxed in pentyl alcohol (30 c.c.) for 6 hr. Potassium carbonate (2 g.) and distilled water were added, and the alcohol was distilled off in steam. The residual liquor was cooled and filtered, and the solid (*C*) washed, the washings being added to the filtrate which was then acidified with 5N-nitric acid; after several hours at room temperature the mixture was again filtered, and chloride ion was determined. The crude cyclisation product (*A*) gave 0·6848 g. and the once crystallised mixture (*B*) gave 0·7000 g. of silver halide; this corresponds to a composition of 56% of 1-chloroxanthone and 44% of 3-chloroxanthone.

In the same manner pure 1-chloroxanthone (2·305 g.) yielded 1·2594 g. of silver chloride (73·7%); pure 3-chloroxanthone gave no trace of silver chloride.

The solid (*C*), on crystallisation from aqueous pyridine, gave 1-*toluene*-p-*sulphonamidoxanthone* as yellow needles, m. p. 168—170° alone and mixed with material prepared from pure 1-chloroxanthone obtained from 1-aminoxanthone (Found: N, 4·1; S, 8·7. $C_{20}H_{15}O_4NS$ requires N, 3·9; S, 8·8%).

1-*Chloroxanthone*.—A mixture of finely divided 1-aminoxanthone (15·7 g.), 10N-hydrochloric acid (210 c.c.), and water (275 c.c.) was stirred at 2° until the hydrochloride was finely divided. Sodium nitrite (6·5 g.) in water (40 c.c.) was added dropwise; in 20 min. all the solid had dissolved. Cuprous chloride solution was prepared by adding a solution of sodium pyrosulphite (16 g.) and sodium hydroxide (10 g.) in water (115 c.c.) at 60° to a stirred solution at the same temperature of cupric sulphate pentahydrate (73 g.) and sodium chloride (25 g.) in water (230 c.c.); the cuprous chloride was washed by decantation and dissolved in 10N-hydrochloric acid (190 c.c.). The diazonium solution was slowly added to the stirred cuprous chloride solution at 40°; after 15 min. the mixture was stirred on the water-bath for 1 hr. and set aside overnight. The pale yellow solid (15·6 g.; m. p. 130°) was collected; crystallisation from aqueous alcohol gave 1-*chloroxanthone* as pale cream needles (12 g.), m. p. 136—137° (Found: C, 67·2; H, 2·9; Cl, 15·4. $C_{13}H_7O_2Cl$ requires C, 67·7; H, 3·0; Cl, 15·4%), $\lambda_{max.}$ 2380 (ε 41,500), 2670 (ε 10,800), 2960 (ε 9000), and 3430 (ε 8300); $\lambda_{min.}$ 2550 (ε 7800), 2900 (ε 1380), and 3020 Å (ε 920).

Treatment of the compound with toluene-*p*-sulphonamide as described above gave 1-toluene-*p*-sulphonamidoxanthone (65%), yellow leaves (from aqueous pyridine), m. p. 168—170° (Found: N, 4·0; S, 9·0%).

3-*Chloroxanthone*.—2 : 4-Dichlorobenzoic acid (38·2 g.), potassium carbonate (55 g.), phenol (47 g.), copper bronze (1·0 g.), cuprous iodide (0·2 g.), and nitrobenzene (150 c.c.) were stirred at 160—165° for 6 hr. The crude dark product on crystallisation from 50% methanol gave 2-carboxy-5-chlorodiphenyl ether as needles (27 g., 55%), m. p. 166° (Found *M*, 250. Calc. for $C_{13}H_9O_3Cl$: *M*, 249). The acid (25 g.) was heated with sulphuric acid (120 c.c.) on the water-bath for ¾ hr., and the solution poured on ice. The precipitate, after extraction with boiling aqueous sodium carbonate, crystallised from a mixture of methanol (500 c.c.), pyridine (60

XUM

c.c.), and water (150 c.c.) to give 3-chloroxanthone (20 g., 87%) as nearly colourless needles, m. p. 130° (Found: Cl, 15·5. Calc. for $C_{13}H_7O_2Cl$: Cl, 15·4%), $\lambda_{max.}$ 2380 (ε 40,500), 2640 (ε 16,200), 2880 (ε 9000), and 3350 Å (ε 7600), $\lambda_{min.}$ 2540 (ε 10,850), 2800 (ε 6450) and 3050 Å (ε 2070).

3-*Methoxyxanthone.*—3-Chloroxanthone (10 g.) was refluxed with a solution from sodium (10 g.) in methanol (500 c.c.) for 72 hr. The solvent was distilled off, water added, the mixture neutralised with dilute sulphuric acid, and the solid (9·0 g.) collected. Crystallisation from dilute ethanol gave 3-methoxyxanthone (7·0 g.), m. p. 128—130° alone and in admixture with material obtained by cyclisation of 2-carboxy-5-methoxydiphenyl ether (Found: C, 74·1; H, 4·5. Calc. for $C_{14}H_{10}O_3$: C, 74·4; H, 4·4%).

Treatment of the crude mixture (4 g.) of 1- and 3-chloroxanthone (obtained by cyclisation of 2-carboxy-3′-chlorodiphenyl ether) in the same manner gave a mixture (3·8 g.) of methoxyxanthones; repeated crystallisation yielded 3-methoxyxanthone (0·9 g.), m. p. and mixed m. p. 128—130° depressed on admixture of 1-methoxyxanthone.

3-*Ethoxyxanthone* was obtained in the same manner in 96% yield as needles (from ethanol), m. p. 146° (Found: C, 75·5; H, 5·1. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%).

3-n-*Butoxyxanthone* was obtained (95%) as pale yellow prisms, m. p. 118° (Found: C, 76·8; H, 5·8. $C_{17}H_{16}O_3$ requires C, 76·2; H, 5·9%).

3-*Phenoxyxanthone.*—3-Chloroxanthone (10 g.) was refluxed with a solution from sodium (10 g.) in phenol (400 g.) for 8 hr. Water (1 l.) was added and 5N-hydrochloric acid to pH 2, and the excess of phenol removed in steam. The *compound* was obtained as needles (9·5 g.; from dilute ethanol), m. p. 116—118° (Found: C, 78·8; H, 4·4. $C_{19}H_{12}O_3$ requires C, 79·1; H, 4·2%).

3-(p-*Methylphenylthio*)*xanthone.*—Thio-*p*-cresol (7·4 g.) was added to a solution from sodium (1·4 g.) in ethanol (160 c.c.); 3-chloroxanthone (9·2 g.) was added and the mixture refluxed for 60 hr. The *product* separated from alcohol–dioxan as colourless needles (12 g.), m. p. 164° (Found: C, 75·5; H, 4·6; S, 9·8. $C_{20}H_{14}O_2S$ requires C, 75·5; H, 4·4; S, 10·1%).

1-*Methoxyxanthone.*—1-Chloroxanthone (2 g.) was refluxed with a solution from sodium (2·0 g.) in methanol (100 c.c.) for 96 hr. 1-Methoxyxanthone (1·4 g.) was isolated in the same manner as needles, m. p. 136° (Found: C, 74·1; H, 4·5%).

Methylation of 1-*Hydroxyxanthone.*—A mixture of 1-hydroxyxanthone (1·15 g.), methyl iodide (4·7 g.), potassium carbonate (1·15 g.), and acetone (25 c.c.) was refluxed for 6 days. The solvent was distilled off, 2N-sulphuric acid (10 c.c.) added, and the mixture extracted with ether (2 × 40 c.c.). The ether layer was shaken with 5N-sodium hydroxide (2 × 10 c.c.), the insoluble sodium derivative of 1-hydroxyxanthone (50 mg.) filtered off, and the ether layer separated, washed with water, and evaporated. Crystallisation of this residue (1·25 g.) twice from alcohol gave unidentified crystals, m. p. 200—202° (Found: C, 64·5; H, 3·2%); the mother-liquors were diluted with water and the precipitate collected. Recrystallisation of this from alcohol gave 1-methoxyxanthone (0·3 g.), needles, m. p. 136° alone and on admixture with a sample prepared from 2-chloro-6-methoxybenzoic acid by the method of Ullmann and Panchaud [10] (Found: C, 74·2; H, 4·4. Calc. for $C_{14}H_{10}O_3$: C, 74·4; H, 4·4%).

2-*Carboxy*-3′ : 5-*dichlorodiphenyl Ether.*—2 : 4-Dichlorobenzoic acid (19·1 g., 0·1 mole), *m*-chlorophenol (26 g., 0·2 mole), copper bronze (0·1 g.), and cuprous iodide (0·1 g.) were added to a solution from sodium (4·6 g., 0·2 g.-atom) in methanol (120 c.c.). The methanol was distilled off and the semi-solid residue placed in an oil-bath at 100° the temperature of which was raised to 180° during 10 min. and held there for a further 15 min. The mixture was cooled and acidified and the excess of *m*-chlorophenol distilled in steam. The residual solid was collected and dissolved in dilute aqueous potassium hydroxide, the solution filtered (charcoal) and acidified, and the acid (25·6 g.; m. p. 120—124°) collected. This was dissolved in warm 2N-sodium hydroxide and the solution chilled; the precipitated sodium salt was filtered off, washed with a little acetone, and redissolved in boiling water, the solution strongly acidified, and the *acid* (20 g.; m. p. 146—148°) collected. It separated from aqueous alcohol in needles, m. p. 147—148° (Found: *M*, 285; Cl, 25·0%. $C_{13}H_8O_3Cl_2$ requires *M*, 283; Cl, 25·1%).

Cyclisation of 2-*Carboxy* 3′ : 5-*dichlorodiphenyl Ether.* 1 : 6- *and* 3 : 6-*Dichloroxanthone.*—The foregoing crude acid (15 g.) was heated with sulphuric acid (150 c.c.) for 1 hr. on the water-bath, and the solution poured on ice. The precipitate was collected and extracted with hot aqueous sodium carbonate, washed with water, and dried; the yield of the mixture of 1 : 6- and 3 : 6-dichloroxanthone was 12·5 g. (m. p. 125—130°).

Crystallisation of this from ethanol seven times yielded 3 : 6-*dichloroxanthone* (3·0 g.) in long

[10] Ullmann and Panchaud, *Annalen*, 1906, **350**, 108.

XUM

colourless prisms, m. p. 184—186° alone and on admixture with unequivocal material obtained from 3 : 6-diaminoxanthone [4] by Julia's method [11] (Found: Cl, 26·6. $C_{13}H_6O_2Cl_2$ requires Cl, 26·8%). Evaporation of the combined mother-liquors gave 9·0 g. of recovered mixture rich in 1 : 6-dichloroxanthone: this was used for the following reaction.

6-Chloro-1-toluene-p-sulphonamidoxanthone.—The foregoing recovered mixture (9·0 g.), toluene-*p*-sulphonamide (9·0 g.), fused sodium acetate (4·5 g.), and copper acetate (0·5 g.) were refluxed (168°) with *n*-hexyl alcohol (112 c.c.) and *sec.*-octyl alcohol (112 c.c.) for 6 hr. The solvents were distilled off in steam and the residual solid (12 g.) extracted with boiling 75% alcohol (250 c.c.) to remove unchanged 3 : 6-dichloroxanthone; the insoluble *6-chloro-1-toluene-p-sulphonamidoxanthone* (9·5 g.) crystallised from 90% pyridine in golden plates (8·5 g.), m. p. 210—212° (Found: N, 3·6; Cl, 9·0; S, 8·2. $C_{20}H_{14}O_4NSCl$ requires N, 3·5; Cl, 8·9; S, 8·0%). This yield indicates that the original crude mixture obtained by cyclisation of 2-carboxy-3′ : 5-dichlorodiphenyl-ether acid contained 52% of 1 : 6- and 48% of 3 : 6-dichloroxanthone.

1-Amino-6-chloroxanthone.—The foregoing sulphonamide (1·5 g.) was heated with 80% sulphuric acid (40 g.) at 150° for 10 min., then at 100° for 10 min., and kept at room temperature overnight. The mixture was poured on ice and excess of aqueous sodium hydroxide, and the precipitate was collected and washed. Crystallisation from alcohol gave *1-amino-6-chloroxanthone* (0·5 g.) in yellow needles, m. p. 164° alone and on admixture with material obtained by cyclisation of 2-carboxy-5-chloro-3′-nitrodiphenyl ether followed by reduction (Found: N, 5·7; Cl, 14·3. $C_{13}H_8O_2NCl$ requires N, 5·7; Cl, 14·5%).

1 : 6-Dichloroxanthone.—This was obtained in 35% yield from 1 : 6-diaminoxanthone [4] by the method described [11] for the 3 : 6-isomeride. The *compound* crystallised from ethanol as colourless needles, m. p. 140—142° (Found: C, 58·9; H, 2·05%).

3 : 6-Dimethoxyxanthone.—3 : 6-Dichloroxanthone (2·5 g.) was refluxed with a solution from sodium (5·0 g.) in methanol (150 c.c.) for 48 hr. The solution was kept on ice overnight, and the crystalline precipitate (2·4 g.; m. p. 184°) collected and washed with cold water. Recrystallisation from methanol gave the pure *compound* in colourless needles, m. p. 184—186° (Found: C, 70·0; H, 4·8. $C_{15}H_{12}O_4$ requires C, 70·4; H, 4·7%).

When the crude cyclisation mixture of 1 : 6- and 3 : 6-dichloroxanthone (4·0 g.) was treated in the same manner, the product (3·8 g.) had m. p. 144—148°; four crystallisations gave 3 : 6-dimethoxyxanthone (1·1 g.), m. p. and mixed m. p. 184°.

6-Chloro-2-nitroxanthone.—A mixture of nitric acid (4·83 c.c.; *d* 1·50; 0·115 mole) and sulphuric acid (25 c.c.) was added during 20 min. to a solution of 3-chloroxanthone (23 g.; 0·1 mole) in sulphuric acid (150 c.c.) stirred at 10—15°. Stirring at room temperature was continued for 2 hr., then at 80° for ½ hr., and the solution was poured on ice. The precipitate was extracted with boiling dilute aqueous sodium carbonate, then with boiling alcohol (300 c.c.), and washed with water; the crude *product* (25 g.; m. p. 240—250°) was pure enough for further use. A sample crystallised from pyridine in buff needles, m. p. 254—256° (Found: N, 5·3; Cl, 12·9. $C_{13}H_6O_4NCl$ requires N, 5·1; Cl, 12·9%). The orientation is based upon the rules previously established [4] for the nitration of xanthones.

2-Amino-6-chloroxanthone.—The foregoing crude compound (20 g.) was added portionwise during 15 min. to a solution of stannous chloride dihydrate (120 g.) in 10N-hydrochloric acid (120 c.c.) stirred at 95°. Stirring was continued at this temperature for a further 105 min. and the mixture set aside. In the morning the mass was drained on sintered glass and the solid stirred with cold 2N-sodium hydroxide (1·5 l.) for 2 hr.; *2-amino-6-chloroxanthone* (17 g.; m. p. 250—260°) was filtered off and washed with water. A sample separated from dilute pyridine in yellow needles, m. p. 268—270° (Found: N, 6·0; Cl, 14·2%).

2-Carboxy-3′-chloro-5-nitrodiphenyl Ether.—*m*-Chlorophenol (12·9 g., 0·1 mole), 2-chloro-4-nitrobenzoic acid (10·1 g., 0·05 mole), copper bronze (0·1 g.), and cuprous iodide (0·1 g.) were added to a solution from sodium (2·3 g.) in methanol (60 c.c.). After removal of the methanol the residue was heated at 110—180° during 15 min. and then at 180° for 15 min. The product (10·0 g.; m. p. 116—118°) crystallised from dilute alcohol in yellow prisms; recrystallisation from toluene–ligroin (b. p. 80—100°) gave the *compound* in yellow needles (8·8 g.), m. p. 120—121° (Found: *M*, 294. $C_{13}H_8O_5NCl$ requires *M*, 293·5).

3- and 1-Chloro-6-nitroxanthone.—The foregoing acid (7·0 g.) was heated on the water-bath with sulphuric acid for 1½ hr. and the solution poured on ice. Recrystallisation of the precipitated mixture (4·8 g.; m. p. 180°) of 3- and 1-chloro-6-nitroxanthone six times from aqueous

[11] Julia, *Bull. Soc. chim. France*, 1952, 546.

pyridine gave 3-*chloro*-6-*nitroxanthone* (1·7 g.) in yellow needles, m. p. 224—226° (Found: N, 5·1; Cl, 12·7. $C_{13}H_6O_4NCl$ requires N, 5·1; Cl, 12·9%). The mother-liquors from the 3rd and 4th crystallisations were diluted with water and the combined precipitates crystallised twice from aqueous pyridine; 1-*chloro*-6-*nitroxanthone* (0·8 g.) was obtained in pale yellow needles, m. p. 214—216° strongly depressed in admixture with the foregoing isomer (Found: N, 5·0; Cl, 12·6. $C_{13}H_6O_4NCl$ requires N, 5·1; Cl, 12·9%).

3-*Amino*-6-*chloroxanthone*.—3-Chloro-6-nitroxanthone (1·7 g.) was stirred at 100° with stannous chloride dihydrate (13·6 g.) and 10N-hydrochloric acid (13·6 c.c.) for 4 hr., and the mixture cooled and stirred with cold 2·5N-sodium hydroxide (300 c.c.) for ½ hour. The precipitate of 3-*amino*-6-*chloroxanthone* (1·0 g.) separated from aqueous-alcoholic pyridine as pale yellow prisms, m. p. 280—282° alone and on admixture with material obtained by cyclisation of 3′-acetamido-2-carboxy-5-chlorodiphenyl ether followed by deacetylation (Found: N, 5·6; Cl, 14·8. $C_{13}H_8O_2NCl$ requires N, 5·7; Cl, 14·5%).

2-*Carboxy*-5-*chloro*-3′-*nitrodiphenyl Ether*.—2 : 4-Dichlorobenzoic acid (19·0 g., 0·1 mole), *m*-nitrophenol (15·3 g., 0·11 mole), potassium carbonate (13·8 g., 0·1 mole), copper bronze (0·1 g.), and cuprous iodide (0·1 g.) were stirred with nitrobenzene (100 c.c.) for 6 hr. at 160—170°. Crystallisation of the crude product (22 g.; m. p. 140—160°) from alcohol gave the *acid* (12 g.), m. p. 180—182° (Found: *M*, 294. $C_{13}H_8O_5NCl$ requires *M*, 293·5).

6-*Chloro*-1-*nitroxanthone*.—The foregoing acid (11 g.) was cyclised by sulphuric acid (88 c.c.) at 100° for 1½ hr. The *product* crystallised from 80% pyridine in pale cream needles (8 g.), m. p. 216° (Found: C, 56·6; H, 2·1; N, 4·9; Cl, 12·8. $C_{13}H_6O_4NCl$ requires C, 56·6; H, 2·1; N, 5·1; Cl, 12·9%).

1-*Amino*-6-*chloroxanthone*.—Reduction of the foregoing compound (5·0 g.), with stannous chloride as described for the 2 : 6-isomer gave 1-*amino*-6-*chloroxanthone* (4·1 g.) which separated from aqueous-alcoholic dioxan in yellow needles, m. p. 164° alone and on admixture with material obtained from 6-chloro-1-toluene-*p*-sulphonamidoxanthone (Found: C, 63·2; H, 3·4; N, 5·9; Cl, 14·7. $C_{13}H_8O_2NCl$ requires C, 63·6; H, 3·3; N, 5·7; Cl, 14·5%).

3′-*Amino- and* 3′-*Acetamido*-2-*carboxy*-5-*chlorodiphenyl Ether*.—80% Hydrazine hydrate (16·5 c.c.) and Raney nickel (*ca.* 0·2 g.) were added to a solution of 2-carboxy-5-chloro-3′-nitrodiphenyl ether (12·9 g.) in ethanol (160 c.c.) stirred at room temperature. The temperature rose to 40° and remained there for 1 hr.; the mixture was stirred at room temperature for 4 hr., then at the b. p. for 2½ hr. The filtered solution was evaporated to dryness, the residual oil dissolved in N-hydrochloric acid (210 c.c.) at *ca.* 70°, and the filtered (charcoal) solution adjusted to pH 3·5 with dilute aqueous sodium hydroxide. The *amino-acid* (10·6 g.; m. p. 158—160°) was collected, washed, and dried at 40°; a sample crystallised from dilute alcohol in needles, m. p. 160° (Found: N, 5·1. $C_{13}H_{10}O_3NCl$ requires N, 5·3%). Acetic anhydride (25·5 g., 23 c.c.) was added dropwise during ½ hour to a solution of the amino-acid (13·4 g.) in 2N-sodiun carbonate vigorously stirred at 25°. The mixture was adjusted to pH 9 with sodium hydroxide, heated to 70°, and filtered (charcoal), and the 3′-acetamido-2-carboxy-5-chlorodiphenyl ether (14·5 g., m. p. 216°) precipitated with hydrochloric acid. A sample crystallised from dioxan in plates m. p. 216—218° (Found: N, 4·7. Calc. for $C_{15}H_{12}O_4NCl$: N, 4·6%).

3- *and* 1-*Amino*-6-*chloroxanthone*.—A solution of the foregoing acetamido-acid (6 g.) in sulphuric acid (60 c.c.) was heated on the water-bath for 2 hr., then cooled, water (16 c.c.) added, and the solution again heated on the water-bath for 1 hr. and poured on ice. After extraction with aqueous sodium carbonate the crude product (4·7 g.) had m. p. 258—260° with much pre-softening. Three crystallisations from pyridine yielded the less soluble 3-amino-6-chloroxanthone (2·3 g.) as pale buff needles, m. p. 280—282° alone and on admixture with a sample obtained from cyclisation of 2-carboxy-3′-chloro-5-nitrodiphenyl ether with subsequent reduction (Found: N, 5·6; Cl, 15·0. Calc. for $C_{13}H_8O_2NCl$: N, 5·7; Cl, 14·5%).

The mother-liquors were evaporated and the residue was crystallised twice from ethanol; 1-amino-6-chloroxanthone (0·25 g.) was obtained as yellow needles, m. p. 164° alone and on admixture with material obtained by hydrolysis of 6-chloro-1-toluene-*p*-sulphonamidoxanthone, but depressed by admixture with the foregoing 3-amino-6-chloro-isomer (Found: N, 5·8; Cl, 14·4. Calc. for $C_{13}H_8O_2NCl$: N, 5·7; Cl, 14·5%).

The authors thank Mr. R. J. Crabbe for technical assistance.

Research Department, Ward, Blenkinsop & Co., Ltd.,
Anglo Estate, Shepton Mallet, Somerset. [*Received, June 5th*, 1958.]

XUM

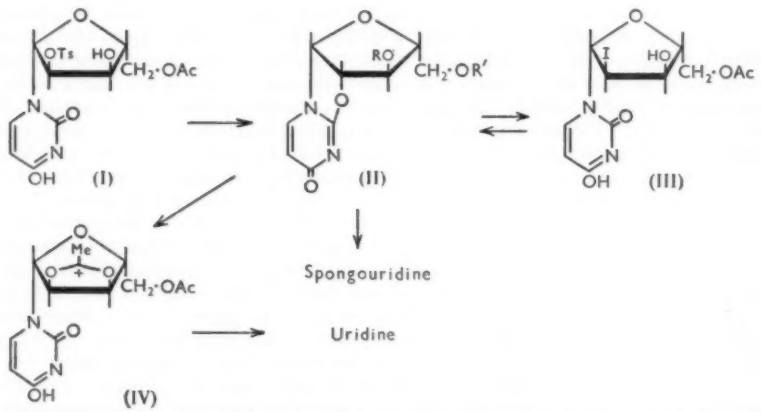
861. *Deoxynucleosides and Related Compounds. Part VIII.*[1] *Some Further Transformations of* O^2 : 2′-cyclo*Uridine.*

By D. M. Brown, D. B. Parihar, and Sir Alexander Todd.

Heating 5′-*O*-acetyl-2′-*O*-toluene-*p*-sulphonyluridine (I) with either sodium azide in methyl cyanide or sodium acetate in acetonylacetone affords 5′-*O*-acetyl-O^2 : 2′-*cyclo*uridine (II; R = H, R′ = Ac). The latter is converted into 5′-*O*-acetyl-2′-deoxy-2′-iodouridine (III) by sodium iodide in acetonylacetone containing glacial acetic acid; the iodide (III), also obtained directly from sulphonyl derivative (I) with sodium iodide, is now assigned the *ribo*-configuration.

3′ : 5′-Di-*O*-acetyl-O^2 : 2′-*cyclo*uridine on acid hydrolysis gives both uridine and spongouridine, in contrast to O^2 : 2′-*cyclo*uridine which gives only the latter. The chemistry of the oxazolidine ring in *cyclo*uridine derivatives is discussed and a possible pathway is suggested for the biochemical conversion of pyrimidine ribo- into deoxyribo-nucleosides.

In the synthesis of the naturally occurring 2′-deoxyuridine described earlier [1] a key step was the conversion of 5′-*O*-acetyl-2′-*O*-toluene-*p*-sulphonyluridine (I) by sodium iodide in acetonylacetone into the 5′-*O*-acetyl-2′-iodo-derivative. The orientation of the iodo-group was not then established. Direct displacement of the toluene-*p*-sulphonyloxy-group would presumably have given an iodo-compound with the *arabo*-configuration, but the greater reactivity of compound (I) than of analogous adenosine derivatives [2] suggested that some other factor was involved in the reaction. Moreover the iodo-compound, like the sulphonate (I), with methanolic ammonia readily gave O^2 : 2′-*cyclo*uridine (II; R = R′ = H), which favoured its formulation as the *ribo*-isomer (III). Evidence which is considered to establish this orientation has now been obtained.



When the sulphonyl derivative (I) was heated with either sodium acetate in acetonylacetone or sodium azide in methyl cyanide, there was no evidence for the introduction of an acetoxy- or azido-group: instead, the sole product was an anhydrouridine acetate. That this was the *cyclo*uridine (II; R = H, R′ = Ac) was evident from its ultraviolet spectrum and the fact that acetylation gave the diacetate (II; R = R′ = Ac) identical with the product of acetylation of O^2 : 2′-*cyclo*uridine [3] itself. The salts had merely

[1] Part VII, Brown, Parihar, Reese, and Todd, *J.*, 1958, 3035.
[2] Unpublished work by Drs. A. M. Michelson and T. L. V. Ulbricht.
[3] Brown, Todd, and Varadarajan, *J.*, 1956, 2388.

buffered the toluene-*p*-sulphonic acid produced in the internal displacement reaction and the non-formation of acetoxy- and azido-compounds is probably to be ascribed, simply, to the low solubility of the salts compared with that of sodium iodide. The formation of the compound (II; R = H, R′ = Ac) in these reactions makes it very probable that the *cyclo*nucleoside derivative was an intermediate in the reaction with sodium iodide too, and that the deoxyiodo-compound was formed by a second displacement on $C_{(2')}$ with opening of the oxazolidine ring. In attempting to establish this it was found that, although the *cyclo*-compound (II; R = H, R′ = Ac) was but little affected by anhydrous hydrogen iodide in methyl cyanide, sodium iodide in acetonylacetone, containing a little glacial acetic acid as buffer, converted it into the deoxyiodo-compound, identical with that obtained by the action of sodium iodide on the toluene-*p*-sulphonate (I). Sodium azide in methyl cyanide re-converted the iodo-compound into the *cyclo*-compound (II; R = H, R′ = Ac). On current views of the mechanism of displacement reactions, these facts allow the assignment of structure (III) to the iodo-compound, and the earlier observations,[1] mentioned above, then find a ready interpretation.

In seeking a further example of a displacement at $C_{(2')}$ with fission of the oxazolidine ring the effect of a neighbouring acetoxy-group was studied. When *O*^{2} : 2′-*cyclo*uridine was hydrolysed with aqueous acid spongouridine was the only product.[3] Hydrolysis of the corresponding diacetate (II; R = R′ = Ac) gave spongouridine and uridine, the latter representing 35% of the total product. Presumably the reaction proceeded, in part, through the intermediate ion (IV) which was hydrolysed without further inversion, as would be expected.[4] The postulated intervention of the neighbouring hydroxyl group in the reaction of *cyclo*uridine with sodium thioethoxide to give the transient intermediate 2′ : 3′-anhydrouridine [5] is now rendered more certain.

Much interest attaches at present to the biosynthetic pathways leading to deoxyribonucleic acid. Evidence has been presented for the conversion of acetaldehyde and triose phosphate into deoxyribose 5-phosphate [6] but the incorporation of the latter into nucleotides has not yet been observed and, at least in one organism, another pathway must also exist.[7] A number of studies lead to the conclusion that the direct conversion of ribonucleosides into deoxyribonucleosides occurs although it is not clear whether this occurs at the nucleoside or the nucleotide level.[8] With regard to the latter possibility, displacement of a group on $C_{(2')}$ in a pyrimidine ribonucleoside to give a *cyclo*nucleoside followed by reductive fission would offer a simple route to the deoxynucleoside. Since Dekker [9] has shown that *cyclo*nucleoside formation can occur by displacement of phosphate on $C_{(2')}$, such a route to deoxynucleosides could have biochemical significance.

Experimental

Unless otherwise stated, butan-1-ol–acetic acid–water (5 : 2 : 3) and Whatman No. 1 paper were used for paper chromatography.

5′-*O*-*Acetyl*-*O*^{2} : 2′-*cyclouridine*.—(*a*) A solution of 5′-*O*-acetyl-2′-*O*-toluene-*p*-sulphonyluridine [3] (0·5 g.) in pure methyl cyanide (15 c.c.) was refluxed with stirring for 4 hr. with powdered sodium azide (327 mg., 4·4 mol.). Sodium toluene-*p*-sulphonate and unchanged sodium azide were removed by filtration, and filtrate and washings were concentrated to a syrup which was evaporated with methanol. After dissolution in warm ethanol and cooling in the ice-box the *product* separated. Recrystallised from ethanol it formed plates (258 mg.),

[4] Winstein and Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2787.
[5] Brown, Parihar, Todd, and Varadarajan, *J.*, 1958, 3028.
[6] Racker, *J. Biol. Chem.*, 1952, **196**, 347; McGeown and Malpress, *Nature*, 1952, **170**, 575.
[7] Lanning and Cohen, *J. Biol. Chem.*, 1955, **216**, 413.
[8] Rose and Schweigert, *ibid.*, 1953, **202**, 635; Roll, Weinfeld, and Carroll, *ibid.*, 1956, **220**, 455; Reichard, *Acta Chem. Scand.*, 1955, **9**, 1275; 1957, **11**, 11; Grossman and Hawkins, *Biochim. Biophys. Acta*, 1957, **26**, 657; Grossman, *Fed. Proc.*, 1958, **17**, 235; Amos and Magasanik, *J. Biol. Chem.*, 1957, **229**, 653; Bagatell, Wright, and Sable, *Biochim. Biophys. Acta*, 1958, **28**, 216.
[9] Dekker, personal communication; see also Abs. Papers, 133rd Amer. Chem. Soc. Meeting, San Francisco 1958, p. 4D.

XUM

m. p. 168—169°, R_F 0·65 (Found: C, 49·4; H, 4·4; N, 10·7. $C_{11}H_{12}O_6N_2$ requires C, 49·25; H, 4·5; N, 10·4%), $\lambda_{max.}$ 248, 224 mμ (ε 7450, 9010), $\lambda_{min.}$ 237 mμ (ε 6800) in 95% EtOH.

(*b*) The above 2′-*O*-toluene-*p*-sulphonyl derivative (0·104 g.) was treated in the same way with freshly fused sodium acetate (0·104 g.) in dry acetonylacetone (4 c.c.) at 100° for 3 hr. The product was isolated as above and formed plates (51 mg.), m. p. 168—169° alone or mixed with O^2 : 2′-*cyclo*uridine-5′-acetate; infrared spectra and R_F values were identical. The substance gave no reaction with the periodate spray reagent on chromatograms.

(*c*) 5′-*O*-Acetyl-2′-deoxy-2′-iodouridine [1] (215 mg.) was heated for 15 hr. with sodium azide (247 mg.) in dry methyl cyanide (10 c.c.), and the solution worked up as above, to give 5′-*O*-acetyl-O^2 : 2′-*cyclo*uridine (116 mg.), R_F 0·65, m. p. and mixed m. p. 169—170° (Found: C, 49·4; H, 4·25; N, 10·8%). The product had infrared and ultraviolet spectra identical with those of the *cyclo*uridine acetate isolated as above.

3′ : 5′-*Di*-O-*acetyl*-O^2 : 2′-cyclo*uridine*.—O^2 : 2′-*cyclo*Uridine (100 mg.) was shaken with dry pyridine (5 c.c.) and acetic anhydride (5 c.c.) for one day. Ethanol (20 c.c.) was added with cooling, solvents were removed *in vacuo*, and the residue was evaporated with ethanol until free from pyridine. The *product* crystallised from dry ethanol (4 c.c.) forming stout prisms (82 mg.), m. p. 186—187°, R_F 0·71 (Found: C, 50·3; H, 4·65; N, 9·1. $C_{13}H_{14}O_7N_2$ requires C, 50·3; H, 4·5; N, 9·0%), $\lambda_{max.}$ 248, 224 mμ (ε 8030, 9725), $\lambda_{min.}$ 238 mμ (ε 7450) in 95% EtOH.

The same substance was obtained by acetylation of 5′-*O*-acetyl-O^2 : 2′-*cyclo*uridine.

Action of Sodium Iodide on 5′-O-*Acetyl*-O^2 : 2′-cyclo*uridine*.—A solution of 5′-*O*-acetyl-O^2 : 2′-*cyclo*uridine (93 mg.), dry sodium iodide (224 mg.) and anhydrous (recrystallised) acetic acid (50 mg.) in acetonylacetone was heated at 100° for 12 hr. with exclusion of moisture. Paper chromatography showed the presence only of starting material and product (*ca.* 60%). The solvents were removed *in vacuo*, the residue was dissolved in water containing a little sodium thiosulphate, and the product isolated by extraction with ethyl acetate (2 × 10 c.c.). Removal of the solvent followed by crystallisation at 0° for 4 days from dry ethanol (2 c.c.) gave the product. On recrystallisation it formed needles (23 mg.), m. p. and mixed m. p. 167—168° with 5′-*O*-acetyl-2′-deoxy-2′-iodouridine.[1] The compounds had identical infrared spectra and R_F values (0·77) on paper chromatograms (pink colour with the cysteine–sulphuric acid spray reagent).

Acid Hydrolysis of 3′ : 5′-*Di*-O-*acetyl*-O^2 : 2′-cyclo*uridine*.—(*a*) The *cyclo*uridine diacetate (20 mg.) was heated in 0·1N-hydrochloric acid for 1 hr. at 100°. The solution was than taken to dryness under reduced pressure, giving a syrup. (*b*) The *cyclo*uridine diacetate (20 mg.) was heated at 100° for 1 hr. with 80% acetic acid, then the solvent was removed. The residual product was deacetylated by treatment with half-saturated methanolic ammonia at room temperature for 8 hr. and the solvent was then removed *in vacuo*, giving a syrup.

Paper chromatography of the products from (*a*) and (*b*) showed the presence in each of two ultraviolet absorbing substances, of R_F 0·44 (periodate positive) and 0·49 (periodate negative), corresponding to uridine and spongouridine. Electrophoresis on paper in borate buffer (pH 10; 260 v for 10 hr.) showed two products migrating 4·9 and 1·2 cm., again corresponding to uridine and spongouridine. The relative amounts, estimated by the optical density of extracts of excised spots, were, for reaction (*a*) 1 : 1·35 and for reaction (*b*) 1 : 2.

Degradation of the reaction products by reduction and hydrolysis [10] gave ribose and ribinose, characterised chromatographically as the only detectable sugars.

This work was carried out during the tenure of an All-India Scholarship (by D. B. P.).

University Chemical Laboratory, Cambridge. [*Received, June 27th*, 1958.]

[10] Burke, *J. Org. Chem.*, 1955, **20**, 643.

862. *Complexes of Titanium and Zirconium Halides with Organic Ligands.*

By H. J. Emeléus and G. S. Rao.

Complexes of titanium tetrafluoride, tetrachloride, tetrabromide, and tetraiodide and of zirconium tetrachloride and tetrabromide with various organic ligands have been prepared. Those of titanium tetraiodide are least readily formed. Dissociation pressures at 80—130° for complexes with selected ligands under comparable conditions diminish in the order fluoride > iodide > bromide > chloride and, for a given ligand and halide, are higher for the zirconium salt than for that of titanium. The difficulties in relating these measurements to the true heats of formation of the complexes are discussed.

Few complexes of titanium tetra-fluoride, -bromide, and -iodide with organic ligands have been described, although for titanium tetrachloride the number is considerable.[1] The present experiments were made to determine if these three halides form compounds similar to those for the tetrachloride and to attempt to determine their relative stabilities from dissociation pressures. A number of compounds of zirconium tetrachloride and tetrabromide with organic ligands were also made and their dissociation pressures are recorded.

The known complexes of titanium tetrachloride include a number with simple inorganic molecules such as ammonia, hydrogen sulphide, nitrosyl chloride, thionyl chloride, and phosphorus halides and oxyhalides. There is virtually no information on the reaction of titanium tetraiodide with these substances. Titanium tetrabromide forms adducts with a few, of formulæ similar to those for titanium tetrachloride (*e.g.*, $TiBr_4,8NH_3$; $TiBr_4,2H_2S$; $2TiBr_4,SO_2$; $TiBr_4,2PH_3$), but only the ammoniates of titanium tetrafluoride are known. The organic ligands which form adducts with the tetrachloride include ethers, sulphides, thiols, esters, acid chlorides, nitriles, amines, and amides whereas titanium tetrabromide forms adducts only with ethers [2] and with several aromatic amines.[3] No pure addition compounds of the tetraiodide with ethers could be isolated,[2] presumably because of their low stability. The only compounds of titanium tetrafluoride with organic ligands are a 1 : 1 compound with ethyl alcohol, which is of interest because the tetrachloride forms alkoxides, and a 1 : 1 pyridine adduct.[4] Zirconium tetrachloride forms addition compounds with much the same range of organic molecules as does titanium tetrachloride, and the tetrabromide is known to form adducts only with ammonia, pyridine, ethylamine, and aniline.

Our preparative work shows that titanium tetrafluoride and tetrabromide form much the same range of addition compounds as does the tetrachloride (see analyses, Tables 3—5). The same is true of the two zirconium halides. Only for titanium tetraiodide is there evidence that the organic ligands may be weakly held. In general, however, the preparations fail to give any indication of the relative stabilities of the products from the metal fluorides, chlorides, and bromides. Three organic compounds, phenol, 2-naphthol, and piperidine, reacted with titanium tetrabromide. This parallels exactly the behaviour of the tetrachloride. The extent of replacement of the halogen is presumably determined both by the conditions and the reactant. Thus, with phenol all four bromine atoms are replaced whereas with 2-naphthol under mild conditions, only two bromine atoms react. Probably these reactive substances would form addition compounds at lower temperatures but the point has not been studied.

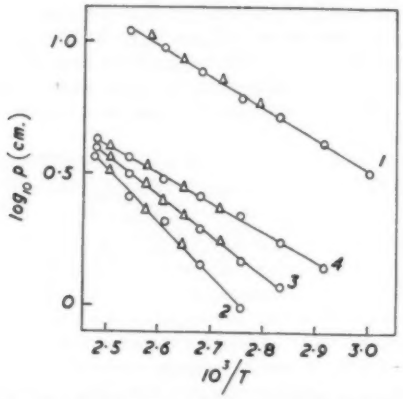
Most of the compounds prepared contain two molecules of ligand per molecule of

[1] See Gmelin's "Handbuch der anorg. Chemie," 1951, No. 41. Titan. See also Ref. 5.
[2] Rolsten and Sisler, *J. Amer. Chem. Soc.*, 1957, **79**, 1068.
[3] Prasad and Tripathi, *J. Indian Chem. Soc.*, 1956, **33**, 837.
[4] Ruff and Ipsen, *Ber.*, 1903, **36**, 1777.

XUM

titanium halide. As excess of ligand was used, the experiments might not show the existence of a 1 : 1 compound. For titanium tetrachloride there are a number of cases in which both the 1 : 1 and 1 : 2 adducts are known (*e.g.*, with diethyl ether and ethanethiol). In a few cases a 1 : 1 adduct only has been described (*e.g.*, $TiCl_4,CH_3{\cdot}COCl$; $TiCl_3,CH_3{\cdot}NO_2$; $TiCl_4,C_2H_5{\cdot}NO_2$), and similar derivatives were obtained from the tetrabromide. With titanium tetrafluoride it is probably significant that in each case, apart from pyridine, only a 1 : 1 compound was obtained. With pyridine, however, Ruff and Ipsen isolated a 1 : 1 compound [4] whereas the present work gave a 1 : 2 compound. Nothing is known about the structures of the compounds with organic ligands except that the majority would have octahedral configurations. All were readily decomposed by water and soluble in organic solvents such as carbon tetrachloride.

Dissociation pressures of selected complexes were measured with an isoteniscope in which a small mercury manometer was used as a null instrument. Attack on the mercury was slight and satisfactory reproducibility was obtained for ascending and descending



1. $TiF_4,2C_5H_5N$
2. $TiCl_4,2C_5H_5N$
3. $TiBr_4,2C_5H_5N$
4. $TiI_4,2C_5H_5N$

○ Ascending temp.
△ Descending temp.

temperatures in the range 80—130°. Typical data are given in the Figure for the 1 : 2 pyridine adducts of the four titanium halides. In each case the plot of log p against $1/T$ was approximately linear.

The data are summarised in Table 1, which gives the constants of the equation $\log_{10} p(\text{cm.}) = C - A/T$.

TABLE I.

Compound	A	C	Compound	A	C	Compound	A	C
$TiF_4,2C_5H_5N$	1200	4·10	$TiCl_4,2CH_3{\cdot}CN$	2700	7·92	$ZrBr_4,2C_2H_5{\cdot}CN$	840	3·33
$TiCl_4,2C_5H_5N$	2075	5·70	$TiBr_4,2CH_3{\cdot}CN$	2230	6·96	$TiF_4,2C_6H_5{\cdot}CN$	1500	4·68
$TiBr_4,2C_5H_5N$	1360	3·99	$ZrCl_4,2CH_3{\cdot}CN$	1500	4·77	$TiCl_4,2C_6H_5{\cdot}CN$	2130	5·92
$TiI_4,2C_5H_5N$ ...	1010	3·14	$ZrBr_4,2CH_3{\cdot}CN$	1205	4·09	$TiBr_4,2C_6H_5{\cdot}CN$	1420	4·21
$ZrCl_4,2C_5H_5N$	1890	5·65	$TiCl_4,2C_2H_5{\cdot}CN$	2430	7·12	$ZrCl_4,2C_6H_5{\cdot}CN$	890	2·79
$ZrBr_4,2C_5H_5N$	1720	5·14	$TiBr_4,2C_2H_5{\cdot}CN$	1840	5·71	$ZrBr_4,2C_6H_5{\cdot}CN$	760	2·49
$ZrBr_4,2C_5H_5N$	1720	5·14	$ZrCl_4,2C_2H_5{\cdot}CN$	1010	3·76			
$TiF_4,CH_3{\cdot}CN$	1650	5·41						

The pyridine adducts of the four titanium halides, which are similarly constituted, have dissociation pressures in the order fluoride > iodide > bromide > chloride. The same order is observed for acetonitrile and benzonitrile adducts of the fluoride, chloride, and bromide, notwithstanding that the fluoride forms only a 1 : 1 compound. The significance of this anomalous position of the fluoride is discussed below. The dissociation pressure curves of the adducts of zirconium tetrabromide adducts were also above those for the tetrachloride, and, for a given halogen and ligand, were higher for zirconium than for titanium. The infrared spectra of most of the compounds were recorded [5] but no

[5] Complete data are given in the Ph.D. Thesis of G. S. Rao (Cambridge University, 1957).

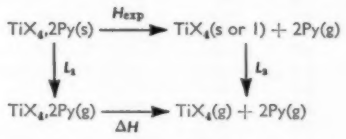
correlation could be found between the small changes in the characteristic frequencies of the ligand molecules resulting from co-ordination and the apparent relative stabilities of the compounds.

Thermodynamic functions can only be derived from these data on certain major assumptions, the first of which is that the complexes are fully dissociated in the vapour phase. The complex $TiCl_4,2POCl_3$ was shown by Payne to be completely dissociated at 80°.[6] Calculation of equilibrium constants is possible only if the dissociation products are in a definite state. Titanium tetraiodide and zirconium tetrachloride and tetrabromide have very small vapour pressures at the maximum temperatures used in the dissociation-pressure measurements and may be treated as solid dissociation products of zero vapour pressure. The vapour pressure of titanium tetrafluoride (b. p. 284°) was <3 mm. at 100° and this has also been assumed to condense completely. The dissociation of the pyridine adduct of titanium tetrafluoride and of the other 1 : 2 adducts of these halides is therefore of the type $AB_2(s) \rightleftharpoons A(s) + 2B(g)$ and the equilibrium constants are given by $K_p = \frac{1}{4}p^2$, where p is the measured dissociation pressure. Titanium tetrachloride and tetrabromide (b. p. 136° and 230°) are assumed to remain in the gas phase. Vapour pressures for the latter have been measured recently.[7] In this case the dissociation equilibrium is of the type $AB_2(s) = A(g) + 2B(g)$ and $K_p = (4/27)p^3$. Variation of K_p with temperature is then given by $\log_{10} K_p = C' - A'/T$. Values of A' and C', and of the derived value of ΔH, ΔG, and ΔS, for the series of pyridine adducts are given in Table 2. Values of K_p are in atmospheres.

TABLE 2.

Compound	A'	C'	ΔH_{exp} (kcal. mole^{-1})	$\Delta G_{298°}$ (kcal. mole^{-1})	ΔS (cal. deg.$^{-1}$ mole^{-1})
$TiF_4,2C_5H_5N$	2400	3·84	11	5·8	18
$TiCl_4,2C_5H_5N$	6225	10·64	28	14	49
$TiBr_4,2C_5H_5N$	4090	5·50	19	11	25
$TiI_4,2C_5H_5N$	2030	1·91	9	6·8	8
$ZrCl_4,2C_5H_5N$	3780	6·93	17	7·9	32
$ZrBr_4,2C_5H_5N$	3430	5·92	16	7·6	27

The values of ΔH_{exp}, the measured enthalpy, again show the anomalous position of the titanium tetrafluoride complex. The relationship between ΔH_{exp}, and ΔH, the enthalpy of formation of the complex in the gas phase, is shown by the annexed Hess's law cycle, L_1 and L_2 being the latent heats of sublimation of the complex and the tetrahalide, respectively. It follows that $\Delta H = \Delta H_{exp} + L_2 - L_1$. It is reasonable to assume that L_1 is approximately the same for the four octahedrally co-ordinated complexes.



The latent heats of sublimation (kcal. mole^{-1}) are known for all the titanium tetrahalides and are: TiF_4 22,[8] $TiCl_4$ 11,[9,10] $TiBr_4$ 12,[7] TiI_4 14.[11] Values of $\Delta H_{theoretical}$ then become $33 - L_1$, $39 - L_1$, $31 - L_1$, and $23 - L_1$, in the order fluoride to iodide, and it is seen that the tetrafluoride complex has a lower heat of formation than the tetrachloride.

It seems impossible at present, particularly in the absence of structural data, to be

[6] Payne, *Rec. Trav. chim.*, 1956, **75**, 620.
[7] Hall, Blocher, and Campbell, *J. Electrochem. Soc.*, 1958, **105**, 271.
[8] *Idem, ibid.*, 1958, **105**, 275.
[9] Kelley, U.S. Bureau of Mines Bulletin No. 393, 1936.
[10] *Idem, ibid.*, No. 383, 1936.
[11] Blocher and Campbell, *J. Amer. Chem. Soc.*, 1947, **69**, 2100.

more precise in the interpretation of such values. The differences cannot be directly related to the energy of the Ti–N bond in this set of complexes since this takes no account of the deformation energies of the donor and acceptor molecules involved in complex formation.

Experimental

Titanium tetrafluoride, prepared by passing fluorine (10 g. per hr.) over titanium turnings (20 g.) in a nickel boat in a nickel tube at 300°, was purified by vacuum sublimation in dry Pyrex at 200—250° (Found: F, 60·5; Ti, 38·9. Calc. for F_4Ti: F, 61·3; Ti, 38·7%). Titanium tetrachloride was purified by fractional distillation *in vacuo* (Found: Cl, 74·4; Ti, 25·4. Calc. for Cl_4Ti: Cl, 74·7; Ti, 25·3%). Titanium tetrabromide, prepared by passing bromine vapour in a stream of nitrogen over a mixture of titanium dioxide and sugar charcoal at 600°, was purified by vacuum distillation (Found: Br, 86·7; Ti, 13·3. Calc. for Br_4Ti: Br, 87·0; Ti, 13·0%). Titanium tetraiodide was prepared by Blocher and Campbell's method [11] (Found: I, 90·7; Ti, 8·8. Calc. for I_4Ti: I, 91·4; Ti, 8·6%). Zirconium tetrachloride and tetrabromide were prepared by passing chlorine, or bromine vapour in pure nitrogen, over a heated mixture of zirconium dioxide and sugar charcoal at 580—600° (Found: Cl, 60·5; Zr, 39·3. Calc. for Cl_4Zr: Cl, 60·9; Zr, 39·1%. Found: Br, 77·5; Zr, 22·4. Calc. for Br_4Zr: Br, 77·8; Zr, 22·2%). All organic ligands and solvents were " AnalaR " or were purified by standard methods. They were dried and distilled *in vacuo* just before use.

Complexes of titanium tetrachloride were made by distilling the halide and a moderate excess of the organic ligand in turn *in vacuo* into a weighed reaction flask cooled in liquid nitrogen. After reaction at 20° the excess of ligand was distilled off, and dry nitrogen was admitted to the flask, which was opened and handled subsequently in a dry-box. Titanium tetrabromide and tetraiodide were introduced into the weighed reaction flask in carbon tetrachloride solution, the solvent being pumped away before reweighing. Most of the organic ligands were again distilled directly on to the halide. A few which were of low volatility were added in an organic solvent. In these cases the excess of ligand was washed away with a solvent in which the adduct did not dissolve appreciably (*e.g.*, benzene). Samples for analysis were taken in the dry-box and decomposed by alkali, the metals being estimated as their dioxides, fluoride as calcium fluoride, the other halides by the Volhard method, and carbon and hydrogen by micro-combustion.

Complexes of Titanium Tetrafluoride.—Analyses of the *compounds* are in Table 3. They did not have definite m. p.s but most showed signs of decomposition between 80° and 200°.

Table 3.

Compound	Found (%)				Required (%)			
	C	H	F	Ti	C	H	F	Ti
$TiF_4.2C_5H_5N$	42·9	4·0	26·6	17·3	42·6	3·5	27·0	17·0
$TiF_4.CH_3{\cdot}CN$	14·6	1·8	45·7	29·5	14·5	1·8	46·1	29·1
$TiF_4.C_2H_5{\cdot}CN$ ...	20·0	3·0	41·3	27·0	20·1	2·8	42·5	26·8
$TiF_4.C_2H_5{\cdot}CN$ ...	37·0	2·3	33·0	21·5	37·0	2·2	33·5	21·2
$TiF_4.CH_3{\cdot}NH_2$ ...	7·9	3·3	48·2	31·4	7·7	3·3	49·0	31·0
$TiF_4.C_2H_5{\cdot}NH_2$ ...	14·1	3·9	44·4	28·8	14·2	4·1	45·0	28·4
$TiF_4.C_2H_5{\cdot}NH_2$ ...	36·9	3·7	34·0	21·9	33·2	3·2	34·9	22·1
$TiF_4.CH_3{\cdot}CHO$ ...	13·1	2·8	44·6	29·1	14·3	2·4	45·2	28·6
$TiF_4.C_6H_5{\cdot}CHO$ ...	36·5	2·6	32·5	21·3	36·5	2·2	33·1	20·9
$TiF_4.(C_2H_5)_2CO$ ...	28·6	4·5	35·6	23·4	28·6	4·8	36·2	22·9
$TiF_4.CH_3{\cdot}NO_2$ ...	6·6	1·5	40·5	26·5	6·5	1·6	41·1	25·9
$TiF_4.C_6H_5{\cdot}NO_2$ ...	29·2	2·2	30·1	20·3	29·2	2·0	30·8	19·5

Dipyridinium Hexafluorotitanate.—The dipyridine complex of titanium tetrafluoride (0·8 g.) was dissolved in 40% hydrofluoric acid (15 ml.), and the solution evaporated at 20° and treated with pyridine (2 ml.) and ether (10 ml.). The white crystalline *dipyridinium hexafluorotitanate* was washed with ether and dried *in vacuo* (Found: F, 35·0; Ti, 15·3. $C_{10}H_{12}N_2F_6Ti$ requires F, 35·4; Ti, 14·9%).

Complexes of Titanium Tetrachloride and Tetrabromide.—Analyses of the *compounds*, are in Table 4.

Substitution Compounds of Titanium Tetrabromide.—(a) *With phenol.* Titanium tetrabromide (1·57 g.) in benzene (10 ml.) and phenol (2·0 g.) in benzene (15 ml.) were mixed in a

dry-box. The red precipitate was washed with benzene and dried *in vacuo* (Found: Br, 15·7; Ti, 9·9. Calc. for $C_{24}H_{21}O_4BrTi$: Br, 16·0; Ti, 9·6%). After prolonged pumping in a high vacuum hydrogen bromide was lost (Found: Ti, 11·7. $C_{24}H_{20}O_4Ti$ requires Ti, 11·4%).

(b) *With 2-naphthol.* The tetrabromide (1·61 g.) and 2-naphthol (4·0 g.) similarly gave a deep-red solid which was washed with benzene (Found: Br, 32·0; Ti, 9·9. $C_{20}H_{14}O_2Br_2Ti$ requires Br, 32·4; Ti, 9·7%).

(c) *With piperidine.* Piperidine (3·32 g.) was distilled *in vacuo* on to titanium tetrabromide (1·60 g.) cooled in liquid nitrogen. On gradual warming the colour changed from brown to green, yellow, and finally to white. The *product* was washed with carbon tetrachloride, benzene

TABLE 4.

	Found (%)		Required (%)		
Compound	Cl or Br	Ti	Cl or Br	Ti	M. p.
$TiCl_4,2C_5H_5N$	40·4	14·2	40·8	13·8	190° (decomp.)
$TiCl_4,2CH_3{\cdot}CN$	51·8	17·9	52·2	17·6	Subl. 80°
$TiCl_4,2C_2H_5{\cdot}CN$	47·2	16·1	47·3	16·0	104°
$TiCl_4,2C_6H_5{\cdot}CN$	35·6	12·4	35·9	12·1	—
$TiBr_4,2C_5H_5N$	60·4	9·4	60·8	9·1	206° (decomp.)
$TiBr_4,2CH_3{\cdot}CN$	69·6	11·0	71·1	10·7	112—114°
$TiBr_4,2C_2H_5{\cdot}CN$	66·7	10·2	67·0	10·0	118—121°
$TiBr_4,2C_6H_5{\cdot}CN$	55·4	8·5	55·7	8·4	190—191° (decomp.)
$TiBr_4,CH_3{\cdot}NO_2$	74·1	11·3	74·6	11·2	57—59°
$TiBr_4,C_6H_5{\cdot}NO_2$	64·9	9·9	65·2	9·8	86—88°
$TiBr_4,CH_3{\cdot}COCl$	79·1	11·0	79·5	10·8	50—51°
$TiBr_4,C_6H_5{\cdot}COCl$	69·5	9·6	69·8	9·4	80—81°
$TiBr_4,C_6H_4(CO_2{\cdot}CH_3)_2$	56·5	9·0	56·7	8·7	150—152°
$TiBr_4,(C_6H_5)_2NH$	59·2	9·2	59·6	8·9	—

and light petroleum (b. p. 60—70°) (Found: C, 62·7; H, 10·7; Ti, 12·3. $C_{20}H_{40}N_4Ti$ requires C, 62·5; H, 10·4; Ti, 12·5%). The product was fairly stable in the atmosphere.

Complexes of Titanium Tetraiodide.—The *compound* $TiI_4,2C_5H_5N$, prepared as already described, was a deep brown solid (Found: I, 70·8; Ti, 6·9. $C_{10}H_{10}N_2I_4Ti$ requires I, 71·2; Ti, 6·7%). In the attempted preparation of solid complexes with acetonitrile, nitromethane, and acetyl chloride, analyses are consistent with the loss of adduct during the removal of excess of uncombined adduct *in vacuo* (Found: I, 87·5; Ti, 8·2. Calc. for $TiI_4,2CH_3{\cdot}CN$: I, 79·6; Ti, 7·5%. Found: I, 86·3; Ti, 8·4. Calc. for $TiI_4,CH_3{\cdot}NO_2$: I, 82·3; Ti, 7·8. Found: I, 82·3; Ti, 8·4. Calc. for $TiI_4,2CH_3{\cdot}COCl$: I, 80·0; Ti, 7·7%). Benzonitrile, nitrobenzene, and benzoyl chloride gave gums which were not analysed.

Pyridinium Hexaiodotitanate.—The pyridine adduct of titanium tetraiodide (1·5 g.) was dissolved in 10 ml. of " AnalaR " hydriodic acid. Dark brown crystals were deposited slowly. They were washed with benzene and light petroleum (Found: C, 13·5; H, 1·4; I, 77·7; Ti, 5·35. Calc. for $C_{10}H_{12}N_2I_6Ti$: C, 12·4; H, 1·2; I, 78·6; Ti, 5·0%).

Complexes of Zirconium Tetrachloride and Tetrabromide.—Analyses of the *compounds* are in Table 5.

TABLE 5.

	Found (%)		Required (%)			Found (%)		Required (%)	
Compound	Cl	Zr	Cl	Zr	Compound	Br	Zr	Br	Zr
$ZrCl_4,2C_5H_5N$	36·0	23·6	36·3	23·2	$ZrBr_4,2C_5H_5N$	56·1	16·2	56·3	16·0
$ZrCl_4,2CH_3{\cdot}CN$	45·0	29·2	45·1	29·0	$ZrBr_4,2CH_3{\cdot}CN$	64·7	18·7	64·9	18·5
$ZrCl_4,2C_2H_5{\cdot}CN$	41·2	26·8	41·4	26·6	$ZrBr_4,2C_2H_5{\cdot}CN$	60·8	17·7	61·4	17·5
$ZrCl_4,2C_6H_5{\cdot}CN$	31·9	20·9	32·3	20·8	$ZrBr_4,2C_6H_5{\cdot}CN$	51·3	14·9	51·9	14·8

Reaction of Titanium Tetrafluoride with Carbon Halides.—Titanium tetrafluoride (1·48 g.) when refluxed with carbon tetrachloride (8·6 g.) for 3 hr. gave trichlorofluoromethane (0·071 g.) (Found: *M*, 132. Calc. for $CFCl_3$: *M*, 137·5). No other volatile product was formed. Titanium tetrafluoride (1·10 g.) was refluxed with carbon tetrabromide (4·12 g.) at 120—125° for 4 hr. The volatile products were dibromodifluoromethane (0·21 g.) (Found: *M*, 200.

XUM

Calc. for CF_2Br_2: *M*, 210), bromotrifluoromethane (0·18 g.) (Found: *M*, 153. Calc. for CF_3Br: *M*, 149), and bromine (0·23 g.). Titanium tetrafluoride (1·0 g.) and carbon tetraiodide (5·1 g.) at 120° for 3 hr. gave trifluoroiodomethane (0·31 g.) (Found: *M*, 187. Calc. for CF_3I: *M*, 196), iodine pentafluoride (0·092 g.) (Found: I : F = 1 : 4·85), and carbon tetrafluoride (0·08 g.) (Found: *M*, 92. Calc. for CF_4: *M*, 88). When titanium tetrafluoride (1·6 g.) and carbon tetraiodide (5·2 g.) were refluxed with carbon tetrachloride (20 g.) the main volatile product was trifluoroiodomethane (Found: *M*, 191. Calc. for CF_3I: *M*, 196). The residue was extracted with carbon tetrachloride and benzene and the extract evaporated and hydrolysed with 2N-sodium hydroxide. Analysis of the hydrolysate showed the formation of the *fluoroiodide* $TiFI_3$ (Found: F, 4·2; I, 84·3; Ti, 9·6. FI_3Ti requires F, 4·3; I, 85·0; Ti, 10·7%).

One of the authors (G. S. R.) thanks the University of Saugar (India) for study leave. They thank Dr. Waddington for his assistance in interpreting the dissociation-pressure data.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, July 7th*, 1958.]

---

863. *Bis-o-phenylene Pyrophosphite: A New Reagent for Peptide Synthesis. Part I. The Preparation of Some o-Phenylene Pyrophosphites.*

By P. C. CROFTS, J. H. H. MARKES, and H. N. RYDON.

The usefulness of tetraethyl pyrophosphite as a reagent for peptide synthesis prompted a search for other, more readily accessible, pyrophosphites. The preparation of one such reagent, *viz.*, bis-*o*-phenylene pyrophosphite, from catechol by a two-stage process, in an overall yield of more than 80% is reported.

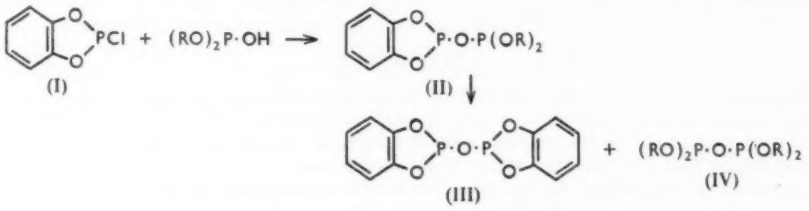
TETRAETHYL PYROPHOSPHITE (IV; R = Et) was introduced as a reagent for the synthesis of peptides by Anderson, Blodinger, and Welcher [1] in 1952 and has since been used in several important syntheses; [2] it suffers, however, from the disadvantages that the yields, both in the preparation of the intermediate, diethyl phosphorochloridite, from phosphorus trichloride and ethanol in the presence of a tertiary base, and in the reaction of this phosphorochloridite with diethyl phosphite, are only moderate, and that purification, particularly of the phosphorochloridite, is difficult. The fact that *o*-phenylene phosphorochloridite (I) is readily prepared,[3] in excellent yield, from catechol and phosphorus trichloride without the use of tertiary base, suggested that *o*-phenylene pyrophosphites might be more readily accessible than the tetraethyl ester.

o-Phenylene phosphorochloridite (I) was at first prepared in ether, as described by Anschütz *et al.*,[3] but later, and more conveniently for large scale working, without a solvent. *o*-Phenylene phosphorochloridite with di-*n*-butyl phosphite and triethylamine in light petroleum gave a moderate yield of di-*n*-butyl *o*-phenylene pyrophosphite (II; R = Bu^n). A similar experiment with diethyl phosphite, however, yielded a mixture from which the two symmetrical compounds, tetraethyl pyrophosphite (IV; R = Et) and bis-*o*-phenylene pyrophosphite (III), were obtained. The expected unsymmetrical compound, diethyl *o*-phenylene pyrophosphite (II; R = Et), was probably also present, but was not isolated; it has recently been prepared from sodium diethyl phosphite and *o*-phenylene phosphorochloridite by Arbusov and Valitova,[4] who also isolated bis-*o*-phenylene pyrophosphite from the reaction product, indicating the occurrence of some

[1] Anderson, Blodinger, and Welcher, *J. Amer. Chem. Soc.*, 1952, **74**, 5309.
[2] *E.g.*, du Vigneaud, Ressler, Swan, Roberts, Katsoyannis, and Gordon, *J. Amer. Chem. Soc.*, 1953, **75**, 4879; Anderson, *ibid.*, 1953, **75**, 6081; du Vigneaud, Ressler, Swan, Roberts, and Katsoyannis, *ibid.*, 1954, **76**, 3115; Ressler and du Vigneaud, *ibid.*, 1957, **79**, 4511; Katsoyannis, Gish, and du Vigneaud, *ibid.*, p. 4516; Gish and du Vigneaud, *ibid.*, p. 3579.
[3] Anschütz, Broeker, Neher, and Ohnheiser, *Ber.*, 1943, **76**, 223.
[4] Arbusov and Valitova, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1956, 681.

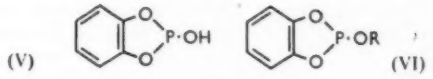
disproportionation. Disproportionations of this kind have been observed on several occasions with derivatives of pyro-acids containing quinquevalent phosphorus.[5]

Attempts were made to confirm the structure of the symmetrical pyrophosphite (III) by preparing it by a different route, the most obvious being reaction between *o*-phenylene phosphite (V) and *o*-phenylene phosphorochloridite in the presence of a tertiary base.



In fact, pure *o*-phenylene phosphite could not be isolated; the attempts to prepare it led, instead, to a very satisfactory preparation of the pyrophosphite (III).

Treatment of *o*-phenylene phosphorochloridite (I) with the theoretical amount of water in the presence of triethylamine dried over potassium hydroxide led to an inseparable mixture of the desired phosphite (V) and catechol. A similar mixture was obtained by the ester-interchange between catechol and diethyl phosphite, although such reactions have been found satisfactory for the preparation of higher dialkyl phosphites.[6] Attempts to prepare the ester (V) by hydrogenolysis of benzyl *o*-phenylene phosphite (VI; R = $Ph{\cdot}CH_2$) were unsuccessful; this may be, at least partly, due to the use of non-hydroxylic solvents, rendered necessary by the susceptibility of the phosphite (VI) to solvolysis.



A further attempt to synthesise bis-*o*-phenylene pyrophosphite was made by heating together the phosphorochloridite (I) and ethyl *o*-phenylene phosphite (VI; R = Et), but this was equally unsuccessful, although analogous reactions have been found very satisfactory for the preparation of pyrophosphates.[7]

When attempting to prepare *o*-phenylene phosphite by hydrolysis of the phosphorochloridite, it was noticed that a little triethylamine hydrochloride was precipitated when triethylamine was added to the ethereal solution of the phosphorochloridite; this was eventually traced to the presence of small amounts of water in the triethylamine dried over potassium hydroxide, no precipitate being formed with triethylamine dried over, and redistilled from, sodium. When this sodium-dried triethylamine was used in a hydrolysis of the phosphorochloridite with slightly less than the theoretical amount of water, the product had a lower melting point than the products of the earlier hydrolysis and was shown, by elementary analysis and by colour reactions, to be a mixture of the phosphite (V) and the pyrophosphite (III).

This result suggested that bis-*o*-phenylene pyrophosphite might be prepared by treatment of two mols. of the phosphorochloridite (I) with one of water, in a manner analogous to the preparation of pyrophosphates by the partial hydrolysis of phosphorochloridates;[8] this proved to be the case. Initially, bis-*o*-phenylene pyrophosphite was prepared in 72% yield by partial hydrolysis of the ester (I) in ether in the presence of triethylamine.

[5] Corby, Kenner, and Todd, *J.*, 1952, 1234; Kosolapoff, *J. Amer. Chem. Soc.*, 1952, **74**, 5520.
[6] Kosolapoff, *J. Amer. Chem. Soc.*, 1951, **73**, 4989; Malowan, *Inorg. Synth.*, 1953, **4**, 61.
[7] Hall and Jacobsen, *Ind. Eng. Chem.*, 1948, **40**, 694; Toy, *J. Amer. Chem. Soc.*, 1949, **71**, 2268; 1950, **72**, 2065.
[8] Toy, *J. Amer. Chem. Soc.*, 1948, **70**, 3882.

XUM

Subsequently, the yield was raised to 87%, and the reaction made more suitable for large-scale operation, by carrying it out without solvent, introducing the water as vapour, and removing the hydrogen chloride under reduced pressure. Bis-*o*-phenylene pyrophosphite (III) is, in this way, readily prepared from catechol by a two-stage process with an overall yield of better than 80%; its use in the synthesis of peptides will be described in Part II of this series.

Experimental

To avoid hydrolysis, calcium chloride guard-tubes were fitted to all condensers and dropping funnels; manipulations were carried out, when necessary, in a dry-box; m. p. tubes were stored over phosphoric oxide. Except where otherwise stated, light petroleum denotes the fraction of b. p. 30—40°. Ether was dried over sodium.

In calculating molecular refractivities, Eisenlohr's values [9] have been used, with 1·643 for oxygen and Kabachnik's value [10] of 7·04 for phosphorus in phosphites.

o-*Phenylene Phosphorochloridite* (I).—Phosphorus trichloride (94 g.) was added, in one portion, to catechol (50 g.) to which water (0·585 g.) had previously been added. There was a brisk evolution of hydrogen chloride and the mixture became solid. After an hour, more phosphorus trichloride (39 g.) was added, and the mixture heated, with stirring, on the steam-bath for 2½ hr. Distillation gave the ester (I) (74·5 g., 94%), b. p. 91°/18 mm., m. p. 30°, n_D^{20} 1·5724 (supercooled liquid).

Di-n-*butyl* o-*Phenylene Pyrophosphite* (II; R = Bu^n).—*o*-Phenylene phosphorochloridite (43·6 g.) in light petroleum (150 ml.) was added, with vigorous stirring, during 10 min. to di-*n*-butyl phosphite (48·5 g.) and triethylamine (25·3 g.) in light petroleum (250 ml.). The mixture was refluxed for 15 min. and allowed to cool. Precipitated triethylamine hydrochloride was removed by rapid filtration and the filtrate kept at 0° for several days. The product was again filtered and distilled; light petroleum and unchanged starting materials were followed by the *pyrophosphite* (27·8 g., 33·5%), b. p. 140°/0·5 mm., n_D^{20} 1·5078, d_4^{20} 1·1760 whence $[R_L]_D$ 84·19 (Calc. 85·55) (Found: C, 49·9; H, 6·3; P, 18·2. $C_{14}H_{22}O_5P_2$ requires C, 50·6; H, 6·7; P, 18·6%).

Reaction of Diethyl Phosphite with o-*Phenylene Phosphorochloridite*.—The phosphorochloridite (43·6 g.) in light petroleum (150 ml.), was added with vigorous stirring during 10 min. to diethyl phosphite (34·5 g.) and triethylamine (25·3 g.) in light petroleum (250 ml.), and the whole refluxed for 15 min. Precipitated triethylamine hydrochloride was filtered off; further hydrochloride was however precipitated slowly and the mixture was refluxed overnight, kept for a few hours, and again filtered. The filtrate, which now remained quite clear, was distilled. The later fractions solidified in the condenser and, on redistillation, gave *bis-o-phenylene pyrophosphite* (16·9 g., 46%), b. p. 122—126°/0·15 mm., m. p. 72° [Found: C, 48·7; H, 3·1; P, 20·6%; *M* (cryoscopic, in benzene), 276. $C_{12}H_8O_5P_2$ requires C, 49·0; H, 2·7; P, 21·0%; *M*, 294]. Several redistillations of the lower-boiling fractions afforded tetraethyl pyrophosphite, b. p. 99—100°/9 mm., n_D^{20} 1·4386 (lit.,[1] n_D^{26} 1·4313) (Found: C, 36·9; H, 7·7; P, 23·2. Calc. for $C_8H_{20}O_5P_2$: C, 37·2; H, 7·8; P, 24·0%).

Ethyl o-*Phenylene Phosphite* (VI; R = Et).—*o*-Phenylene phosphorochloridite (34·9 g.) in ether (50 ml.) was added with rapid stirring during 28 min. to ethanol (9·2 g.) and diethylaniline (30·0 g.) in ether (150 ml.). After being stirred for a further 30 min., the mixture was kept overnight at 0° and filtered. Distillation of the filtrate gave the phosphite (32·7 g., 89%), b. p. 97°/14 mm., n_D^{20} 1·5196, d_4^{20} 1·1954, whence $[R_L]_D$ 46·80 (Calc., 46·41) (lit.,[11] b. p. 86°/11 mm., n_D^{17} 1·5085) (Found: C, 52·2; H, 4·9; P, 16·4. Calc. for $C_8H_9O_3P$: C, 52·2; H, 4·9; P, 16·8%).

There was no reaction, below 200°, when this compound was heated with *o*-phenylene phosphorochloridite, even in the presence of iodine, sodium iodide, or copper powder.

Benzyl o-*Phenylene Phosphite* (VI; R = Ph·CH_2).—*o*-Phenylene phosphorochloridite (34·9 g.) in ether (100 ml.) was added with stirring during 30 min. to benzyl alcohol (21·6 g.) and diethylaniline (30·0 g.) in ether (200 ml.). The mixture was stirred and refluxed for 30 min., then kept at 0° for several days. Filtration, followed by two distillations, afforded the

[9] Eisenlohr, *Z. phys. Chem.*, 1910, **75**, 585.
[10] Kabachnik, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1948, 219.
[11] Arbusov and Valitova, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1940, 529.

XUM

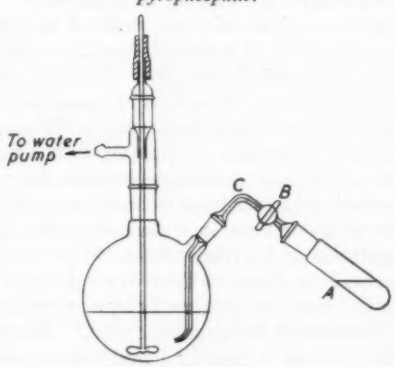
phosphite (35·0 g.; 71%), b. p. 97°/0·13 mm., n_D^{20} 1·5761, d_4^{20} 1·2313, whence $[R_L]_D$ 66·18 (Calc. 65·90) (Found: C, 63·9; H, 4·8; P, 12·8. $C_{13}H_{11}O_3P$ requires C, 63·4; H, 4·5; P, 12·6%).

Attempted Preparations of o-Phenylene Phosphite.—(a) *By hydrogenolysis.* No hydrogen was absorbed when benzyl *o*-phenylene phosphite was shaken with hydrogen in ether over palladised barium sulphate, palladised calcium carbonate, or Adams platinic oxide catalyst, or in dioxan or chloroform over Adams catalyst.

(b) *By ester interchange.* Catechol (22·0 g.) and diethyl phosphite (55·2 g.) were heated together with stirring for 56 hr., the pressure being reduced from atmospheric to 4 mm. until distillation of ethanol ceased. The distillate, collected in a trap at −70°, contained some diethyl phosphite and was estimated from the refractive index to contain 12·7 g. of ethanol (theor., 18·4 g.). Distillation of the residue afforded diethyl phosphite and a solid, b. p. *ca.* 110°/0·3 mm. (Found: P, 15·6. Calc. for $C_6H_5O_3P$: P, 19·8%), which, after recrystallisation from ether–light petroleum, had m. p. 98—106°, depressed to 70—100° on admixture with catechol (m. p. 105°). Addition of ethereal ferric chloride to an ethereal solution gave a deep red-brown colour which faded rapidly to reveal a cream-coloured precipitate; addition of more ethereal ferric chloride gave a permanent red-brown colour. With ethereal ferric chloride, catechol and diethyl phosphite give a red colour and a cream-coloured precipitate respectively. It was concluded that the product was a mixture of catechol and the required phosphite.

(c) *By hydrolysis.* (i) Addition of the theoretical amount of water, in ether, to *o*-phenylene phosphorochloridite and triethylamine (dried over potassium hydroxide and redistilled) in ether, filtration, and distillation of the filtrate gave a white solid, b. p. 160—170°/12 mm., m. p. 103—104°, depressed to *ca.* 85° on admixture with catechol; this material contained phosphorus (Found: P, 14·9%) and behaved towards ethereal ferric chloride in the same way as the product of the previous experiment.

Apparatus for preparation of bis-o-phenylene pyrophosphite.



(ii) Water (1·4 g., 0·078 mole) in ether (150 ml.) was added with stirring during 30 min. to *o*-phenylene phosphorochloridite (14·1 g., 0·081 mole) and triethylamine (dried and distilled over sodium) (9·1 g., 0·090 mole) in ether (270 ml.), and the mixture was stirred and refluxed for a further 30 min. Next day, triethylamine hydrochloride was removed and the filtrate distilled, affording a fraction (3·1 g.), b. p. 130—144°/0·25 mm., m. p. 54—55°, after softening at 44°; the product gave, with ethereal ferric chloride, a pale buff precipitate, and then, on addition of more ferric chloride, a brown oil, but not the intense red-brown solution characteristic of catechol. These reactions, together with elementary analysis (Found: C, 48·4; H, 3·2; P, 20·4. Calc. for $C_6H_5O_3P$: C, 46·2; H, 3·2; P, 19·8. Calc. for $C_{12}H_8O_5P$: C, 49·0; H, 2·7; P, 21·0%), indicated that the product was a mixture of *o*-phenylene phosphite and bis-*o*-phenylene pyrophosphite.

Bis-o-phenylene Pyrophosphite (III).—(a) *With added base.* Water (1·15 g.) in ether (150 ml.) was added with rapid stirring during 45 min. to *o*-phenylene phosphorochloridite (22·7 g.) and triethylamine (dried and distilled over sodium) (14·5 g.) in ether (250 ml.), and the mixture stirred and refluxed for a further 2½ hr. Next day, triethylamine hydrochloride was filtered off and the filtrate evaporated to dryness under reduced pressure, further amounts of hydrochloride being removed by filtration from time to time. The residue (15·6 g.) was recrystallised from light petroleum (b. p. 40—60°), giving the pyrophosphite (13·5 g., 72%), m. p. 72°, not depressed on admixture with material obtained from the phosphorochloridite and diethyl phosphite.

(b) *Without base or solvent (preferred procedure).* The apparatus used is shown in the Figure. *o*-Phenylene phosphorochloridite (144 g.) was placed in the flask and warmed to 30—35°. Water (6·80 g.) was placed in the vessel *A*, the apparatus was evacuated by means of a water-pump, and the tap *B* opened to allow the introduction of water-vapour through tube *C* (1 mm. internal diameter), which occupied 5½ hr. (N.B.: If the water is added too rapidly, the yield

XUM

is reduced.) Vigorous stirring was maintained throughout. Distillation gave recovered phosphorochloridite (20·4 g.) and the pyrophosphite (90·7 g., 87%), b. p. 156°/0·25 mm., m. p. 72°, n_D^{20} 1·5090, d_4^{20} 1·4134 (supercooled liquid), whence $[R_L]_D$ 70·13 (Calc. 70·51); the product obtained by Arbusov and Valitova [4] had n_D^{20} 1·5502, d^{20} 1·3107 (whence $[R_L]_D$ 71·50), was too hygroscopic for the m. p. to be determined and appears to have been impure.

We are grateful to Mr. V. Manohin for the microanalyses and to the Jamaican Government for a scholarship (J. H. H. M.).

MANCHESTER COLLEGE OF SCIENCE AND TECHNOLOGY,
MANCHESTER, 1.

[*Received, July 8th*, 1958.]

---

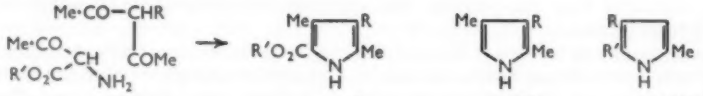
864. *The Synthesis of Tri- and Tetra-alkylpyrroles.*

By A. W. JOHNSON, E. MARKHAM, R. PRICE, and K. B. SHAW.

Some tri- and tetra-alkylpyrroles have been prepared by modifications of the Knorr synthesis. Benzyl esters in the pyrrole series have been subjected to a one-stage hydrogenolysis and decarboxylation in order to remove the ester group.

TRI- and TETRA-ALKYLPYRROLES are useful synthetic intermediates but their preparation frequently is tedious and involves several stages. Application of direct Knorr syntheses gives only low yields of trialkylpyrroles, *e.g.*, 2 : 3 : 5-trimethylpyrrole from the condensation of 3-aminobutan-2-one and acetone [1] and the product is contaminated with the symmetrical pyrazine. On the other hand better yields of pyrroles are obtained from Knorr condensations of α-amino-ketones with β-keto-esters, but the products contain ester and acyl substituents and additional stages are necessary to prepare the alkylpyrroles. Such an approach is exemplified in a detailed preparation of crytopyrrole [2] although the use of lithium aluminium hydride for reduction of ester and acyl groups in the pyrrole series is a further improvement on existing methods.[3] Another variant is the introduction of methyl groups into dialkylpyrroles by formylation and subsequent reduction.[4] The synthesis of pyrroles containing propionic acid or ester groupings has been achieved by an acid-catalysed addition of acrylic ester to the preformed pyrrole ring in certain favourable cases [5] but more frequently by a several-stage process involving formylation and subsequent condensation with malonic acid.[6] Likewise the preparation of pyrroles containing acetic ester groups is usually a multi-stage process.

In a recent paper,[7] we described the use of 3-alkylpentane-2 : 4-diones in pyrrole syntheses where reactions with α-aminoacetoacetic esters (*e.g.*, to form I; R = Me) were not of the usual Knorr type:



(I) (II) (III)

This reaction has now been utilised to provide a convenient route to trisubstituted pyrroles. Condensation of *tert.*-butyl [8] or, better, benzyl α-aminoacetoacetate [9] gave the pyrroles

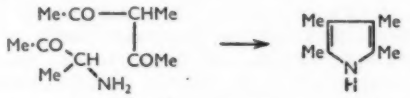
[1] Piloty and Hirsch, *Annalen*, 1913, **395**, 68.
[2] Fischer, *Org. Synth.*, 1955, Coll. Vol. III, p. 513.
[3] Treibs *et al.*, *Annalen*, 1952, **577**, 139; 1954, **589**, 188.
[4] Fischer and Treibs, *Ber.*, 1927, **60**, 380.
[5] Treibs and Michl, *Annalen*, 1954, **589**, 163.
[6] Fischer *et al.*, *Ber.*, 1924, **57**, 602; *Annalen*, 1924, **439**, 180.
[7] Bullock, Johnson, Markham, and Shaw, *J.*, 1958, 1430.
[8] Treibs and Hintermeier, *Chem. Ber.*, 1954, **87**, 1167.
[9] MacDonald, *J.*, 1952, 4176.

XUM

(I; R′ = Bu^t or CH_2Ph) from which the *tert.*-butyl ester group could be removed in one stage by pyrolysis [8] and the benzyl ester group in one stage by hydrogenolysis and decarboxylation in the presence of Raney nickel usually at <120° under pressure (above this temperature, reduction of the trialkylpyrroles was liable to occur although the presence of an ester group in the side-chain appeared to have a stabilising effect). In this manner a variety of trisubstituted pyrroles (II; R = Me, Et, CO_2Et, Ac, $CH_2{\cdot}CO_2Et$, and $CH_2{\cdot}CH_2{\cdot}CO_2Me$) has been prepared in overall yields of the order of 40—60%.

A variation of the reaction, *viz.*, condensation of benzyl acetoacetate with alkyl 1-aminoalkyl ketones gave the benzyl 2 : 4-dialkyl-5-methylpyrrole-3-carboxylates from which 2 : 3 : 5-trisubstituted pyrroles (III; R = Me, Et, R′ = Me; R = Me, R′ = Et) were obtained by removal of the ester group as before.

Finally, by condensation of the 3-alkylpentane-2 : 4-diones with 1-aminoalkyl methyl ketones, the tetrasubstituted pyrroles (2 : 3 : 4 : 5-tetramethyl- and 2-ethyl-3 : 4 : 5-trimethyl-pyrrole) have been obtained in one stage. Tetra-alkylpyrroles have usually been prepared hitherto by insertion of an additional alkyl group into trisubstituted pyrroles, *e.g.*, by direct methylation,[10] by formylation and reduction,[11,12] or by aminomethylation and subsequent reduction.[13]



Experimental

Preparation of Benzyl 3 : 4 : 5-Trisubstituted Pyrrole-2-carboxylates.—Benzyl 3 : 4 : 5-trimethylpyrrole-2-carboxylate. A solution of sodium nitrite (29 g.) in water (60 c.c.) was added with stirring during 30 min. to benzyl acetoacetate (67·5 g.) in glacial acetic acid (140 c.c.) at <10°. The cooled mixture was stirred for a further 4 hr., then kept overnight at room temperature. This solution was added to 3-methylpentane-2 : 4-dione (40 g.) in acetic acid (140 c.c.) in the presence of zinc dust (46 g.) with stirring, while the temperature was kept at about 70°. After the addition, the product was heated under reflux for 15 min., then poured on crushed ice (*ca.* 1 kg.). The crude *ester* was separated, washed with water, and crystallised from ethanol as needles (41·0 g., 45·5%), m. p. 119—120° (Found: C, 73·9; H, 6·85; N, 5·7. $C_{15}H_{17}O_2N$ requires C, 74·05; H, 7·05; N, 5·8%).

By similar condensations the following pyrrole esters have also been prepared. *Benzyl 4-ethyl-3 : 5-dimethylpyrrole-2-carboxylate* [from 3-ethylpentane-2 : 4-dione (see below)], needles, m. p. 103° (34%) (Found: C, 74·6; H, 7·65; N, 5·3. $C_{16}H_{19}O_2N$ requires C, 74·7; H, 7·45; N, 5·45%). *Benzyl 4-ethoxycarbonylmethyl-3 : 5-dimethylpyrrole-2-carboxylate* [from ethyl 3-acetyl-4-oxopentanoate (see below)], fine needles (38%), m. p. 76—78° (Found: C, 68·8; H, 6·9; N, 4·65. $C_{18}H_{21}O_4N$ requires C, 68·6; H, 6·7; N, 4·45%). *Benzyl 4 : 2′-methoxycarbonylethyl-3 : 5-dimethylpyrrole-2-carboxylate* [from methyl 4-acetyl-5-oxohexanoate (see below)], needles (42%), m. p. 99—101° (Found: C, 68·7; H, 6·65; N, 4·05. $C_{18}H_{21}O_4N$ requires C, 68·6; H, 6·7; N, 4·45%). *Benzyl 4-acetyl-3 : 5-dimethylpyrrole-2-carboxylate* (by a normal Knorr condensation from acetylacetone and benzyl α-aminoacetoacetate), needles (52%), m. p. 135° (Found: C, 70·9; H, 6·0; N, 5·15. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·3; N, 5·2%). *Benzyl 4-ethoxycarbonyl-3 : 5-dimethylpyrrole-2-carboxylate* (similarly from ethyl acetoacetate and benzyl α-aminoacetoacetate), needles (61%), m. p. 120—121° (Found: C, 67·4; H, 6·0; N, 4·75. $C_{17}H_{19}O_4N$ requires C, 67·75; N, 6·3; N, 4·65%).

Preparation of Benzyl 2 : 4 : 5-Trisubstituted Pyrrole-3-carboxylates.—Benzyl 2 : 4 : 5-trimethylpyrrole-3-carboxylate. A solution of 1-hydroxyiminoethyl methyl ketone [14] (185 g.) in glacial acetic acid (750 c.c.) was added to benzyl acetoacetate (350 g.) in acetic acid (800 c.c.) in the presence of zinc dust (234 g.) during 90 min. with stirring, the temperature being kept as close to 70° as possible. The mixture was then heated under reflux for 1 hr. and poured on

[10] Fischer and Bartholomäus, *Z. physiol. Chem.*, 1912, **80**, 10.
[11] Fischer and Walach, *Annalen*, 1926, **450**, 109.
[12] Treibs and Scherer, *ibid.*, 1954, **589**, 196; MacDonald and Michl, *Canad. J. Chem.*, 1956, **34**, 1671.
[13] Treibs and Zinmeister, *Chem. Ber.*, 1957, **90**, 87.
[14] Semon and Damerell, *Org. Synth.*, Coll. Vol. II, 1943, p. 204.

crushed ice (5 kg.). The crude *ester* was separated, washed, and crystallised from aqueous ethanol; it formed needles (228 g., 51%), m. p. 85—86° (Found: C, 74·4; H, 7·0; N, 6·15. $C_{14}H_{17}O_2N$ requires C, 74·05; H, 7·05; N, 5·76%). *Benzyl 4-ethyl-2 : 5-dimethylpyrrole-3-carboxylate*, prepared (40·5%) by a similar method from diethyl ketone, had m. p. 88—89° (Found: C, 74·4; H, 7·4; N, 5·4. $C_{16}H_{19}O_2N$ requires C, 74·7; H, 7·45; N, 5·45%). *Benzyl 5-ethyl-2 : 4-dimethylpyrrole-3-carboxylate* (37%), needles (from ethanol), m. p. 126—127°, was obtained similarly from methyl *n*-propyl ketone (Found: C, 74·3; H, 7·4; N, 5·5%).

Preparation of Trisubstituted Pyrroles.—Hydrogenolysis and decarboxylation of benzyl esters. 2 : 3 : 4-Trimethylpyrrole. Benzyl 3 : 4 : 5-trimethylpyrrole-2-carboxylate (20 g.) was dissolved in methanol (100 c.c.), and methanol-washed Raney nickel (5 g.) was added. The mixture was hydrogenated at 150—160°/140 atm. for 2 hr., after which the catalyst and solvent were removed. The residue was distilled under reduced pressure, and the fraction of b. p. 78—85°/12 mm. collected as a colourless oil (lit.,[15] b. p. 71—72°/11 mm. for 2 : 3 : 4-trimethylpyrrole) which solidified (m. p. 36—38°) (4·1 g., 46%). The picrate formed yellow prisms, m. p. 139—141° (lit.,[16] m. p. 140°), from ethanol (Found: C, 46·5; H, 4·4; N, 16·2. Calc. for $C_{13}H_{14}O_7N_4$: C, 46·2; H, 4·2; N, 16·5%).

By similar reactions at 110—120°/100 atm. for 2 hr. the following trisubstituted pyrroles have also been prepared from the appropriate benzyl esters. Cryptopyrrole (80%), b. p. 84—87°/12 mm. (lit.,[2] b. p. 85·5—87°/12·5 mm.) (Found: C, 77·9; H, 10·7. Calc. for $C_8H_{13}N$: C, 78·0; H, 10·65%), $\lambda_{max.}$ (in EtOH) 213 mμ (log ε 3·85) [picrate, yellow needles, m. p. 138° from ethanol (lit.,[17] 137·5°)]. 2 : 3 : 5-Trimethylpyrrole (58%), b. p. 72—74°/10—11 mm. (lit.,[16] b. p. 75·5—76·5°/16 mm.) (Found: C, 76·8; H, 9·9. Calc. for $C_7H_{11}N$: C, 77·0; H, 10·15%). 3-Ethyl-2 : 5-dimethylpyrrole (66·5%), b. p. 115—117°/60 mm. (lit.,[18] b. p. 121°/63 mm.) (Found: C, 78·0; H, 10·4; N, 11·2. Calc. for $C_8H_{13}N$: C, 78·0; H, 10·65; N, 11·35%). 2-Ethyl-3 : 5-dimethylpyrrole (63%), b. p. 112—114°/63 mm. (lit.,[19] b. p. 93—94°/21 mm.) (Found: C, 77·8; H, 10·6%). 3-Acetyl-2 : 4-dimethylpyrrole (55%), plates (from ethanol), m. p. 135—137° (lit.,[20] 137°), b. p. 170—173°/12 mm. (Found: C, 70·4; H, 7·9; N, 10·3. Calc. for $C_8H_{11}ON$: C, 70·05; H, 8·1; N, 10·2%). 3-Ethoxycarbonyl-2 : 4-dimethylpyrrole (66%), plates (from ethanol), m. p. 76° (lit.,[8] m. p. 75—76°), sublimes at 150°/9 mm. *3-Ethoxycarbonylmethyl-2 : 4-dimethylpyrrole* (19%), b. p. 140—146°/9 mm. (Found: C, 66·0; H, 8·15. $C_{10}H_{15}O_2N$ requires C, 66·25; H, 8·35%). 3-2′-Methoxycarbonylethyl-2 : 4-dimethylpyrrole (62%) was obtained as an oil, b. p. 144—146°/9 mm. (lit.,[21] b. p. 151°/12 mm.), m. p. 47°. The picrate formed yellow prisms (from ethanol), m. p. 106—108° (lit.,[21] m. p. 107—108°) (Found: C, 46·8; H, 4·5; N, 13·3. Calc. for $C_{16}H_{15}O_9N_4$: C, 46·8; H, 4·4; N, 13·65%).

Thermal Decomposition of tert.*-Butyl Esters.—2 : 3 : 4-Trimethylpyrrole.* A mixture of *tert.*-butyl 3 : 4 : 5-trimethylpyrrole-2-carboxylate [7] (30·9 g.) and toluene-*p*-sulphonic acid (0·1 g.) was heated at 210° until decomposition ceased. The residue was distilled under reduced pressure and the fraction of b. p. 76—80°/12 mm. collected (7·6 g., 46%); it solidified. The picrate, m. p. 138—140° (from ethanol), was identical with the product described above.

Cryptopyrrole. tert.-Butyl 3-acetyl-2 : 4-dimethylpyrrole-2-carboxylate [8] (23·7 g.), 90% hydrazine hydrate (10 c.c.), potassium hydroxide (25 g.), and ethylene glycol (150 c.c.) were heated under gentle reflux for 1 hr. Excess of water was then distilled off until the temperature of the mixture rose to 175—180°, then the mixture was heated under reflux for a further 3 hr. The solution was cooled, diluted with water (100 c.c.), and steam-distilled in an atmosphere of nitrogen until the distillate gave only a faint Ehrlich reaction. The distillate was extracted with ether (3 × 50 c.c.), the ethereal layer dried, and the solvent removed. Distillation of the residue gave cryptopyrrole (1·0 g., 8%), b. p. 93—98°/17 mm. (picrate, m. p. 136°, identical with the product obtained as above).

Preparation of Tetrasubstituted Pyrroles.—2 : 3 : 4 : 5-Tetramethylpyrrole. 1-Hydroxyiminoethyl methyl ketone (42 g.) in glacial acetic acid (150 c.c.) was added to 3-methylpentane-2 : 4-dione (52·5 g.) in acetic acid (250 c.c.) in the presence of zinc dust (54·5 g.) during 45 min. with

[15] Fischer and Walach, *Annalen*, 1926, **447**, 38.
[16] Piloty and Hirsch, *ibid.*, 1913, **395**, 63.
[17] Fischer and Bartholomäus, *Ber.*, 1912, **45**, 1979.
[18] Hess, Wissing, and Suchier, *Ber.*, 1915, **48**, 1865.
[19] Knorr and Hess, *Ber.*, 1911, **44**, 2758; 1912, **45**, 2626.
[20] Fischer and Ernst, *Ber.*, 1926, **59**, 140.
[21] Fischer and Röse, *Ber.*, 1912, **45**, 3274.

XUM

stirring while the temperature was kept at 65—70°. The mixture was then heated under reflux for 2 hr., after which water (500 c.c.) was added and the product distilled in steam until the distillate no longer gave a positive Ehrlich test (hot). The product was separated from the distillate (*ca.* 1 l.), washed, and dried *in vacuo*, being obtained as colourless plates (22·5 g., 44%), m. p. 109—110° (lit.,[11] m. p. 112°) (Found: C, 78·0; H, 10·6. Calc. for $C_8H_{13}N$: C, 78·0; H, 10·65%), $\lambda_{max.}$ 219 mμ (log ε 3·74).

By a similar method from 1-hydroxyimino-*n*-propyl methyl ketone there was produced 2-ethyl-3 : 4 : 5-trimethylpyrrole (17%) as a pale yellow oil, b. p. 110—114°/25 mm. (lit.,[11] b. p. 114—115°/27 mm.), which solidified. The picrate formed yellow plates (from ethanol), m. p. 102—104° (lit.,[11] m. p. 104°) (Found: C, 49·2; H, 4·9; N, 15·2. Calc. for $C_{15}H_{18}O_7N_4$: C, 49·2; H, 4·95; N, 15·3%).

3-Ethylpentane-2 : 4-dione.—Acetylacetone (66·8 c.c.), ethyl iodide (60 c.c.), anhydrous potassium carbonate (84 g.), and dry acetone (74 c.c.) were heated under reflux on the water-bath for 24 hr. The product was cooled, the solid separated, and the residue distilled. The fraction of b. p. 178—182°/760 mm. (lit.,[22] b. p. 178—179°) (48 g.) was collected. By a similar process using methyl iodide (50 c.c.), 3-methylpentane-2 : 4-dione was prepared, having b. p. 170—172°/760 mm. (56 g.).

Ethyl 3-Acetyl-lævulate.—The sodio-derivative of acetylacetone was treated with ethyl bromoacetate following Garner, Reddick, and Fink's directions.[23] The product was obtained as a colourless oil (48%), b. p. 165°/55 mm.

Methyl 4-Acetyl-5-oxohexanoate.—Acetylacetone was treated with methyl acrylate as described [7] for the ethyl ester. The product was a pale yellow oil (48%), b. p. 142—148°/14 mm. (lit.,[24] b. p. 153—155°/19 mm.).

We acknowledge the award of Maintenance Grants (to E. M. and K. B. S.) from the Department of Scientific and Industrial Research and we thank the directors of Imperial Chemical Industries Limited, Dyestuffs Division, for permission for one of us (R. P.) to take part in this work. Generous gifts of intermediates from the Distillers Company Ltd. are also gratefully acknowledged.

UNIVERSITY OF NOTTINGHAM. [*Received, July 15th,* 1958.]

[22] von Auwers and Jacobsen, *Annalen*, 1921, **426**, 227.
[23] Garner, Reddick, and Fink, *J. Amer. Chem. Soc.*, 1909, **31**, 668.
[24] March, *Ann. Chim.* (*France*), 1902, **26**, 333.

---

865. *Investigations on the Co-ordinative Power of Uranyl. Part III.* Infrared Spectra of Some Complexes with β-Diketones.*

By L. SACCONI, G. CAROTI, and P. PAOLETTI.

Infrared absorption spectra have been obtained for a number of uranyl complexes with acetylacetone, benzoylacetone, and dibenzoylmethane, crystallised with water, ammonia, or pyridine and in the anhydrous state. Despite the complexity of the spectra the two ν_1 and ν_3 frequencies assigned to the bent form of the uranyl group have been observed for some of such compounds. In the anhydrous complexes of benzoylacetone and dibenzoylmethane such frequencies are shifted and altered in intensity probably owing to the modified crystal field of the " surroundings " of uranyl. The frequencies and the features of the absorption bands of water indicate different types of hydrogen bonding and confirm the existence of co-ordinate bonds between uranium and water molecules in the hydrated complexes. The H–N stretching vibrations of the ammonia appear to be shifted to lower frequencies, a feature regarded as characteristic of nitrogen-to-metal bonds.

A MOST interesting problem in the chemistry of uranium is that of the stereochemistry of the uranyl group. Although *X*-ray diffraction indicates that the UO_2 radical is

* Part II, Sacconi and Giannoni, *J.*, 1954, 2751.

linear,[1-3] Raman and infrared spectra even if not unambiguous, appear to favour a bent form.[4-7]

The structure of the uranyl radical is closely related to the co-ordination number and the nature of co-ordinate bonds of which this radical is capable. Data show that in some uranyl compounds, *e.g.*, the nitrate, the uranium atom is octaco-ordinated, and that the central atom forms six bonds which have some degree of covalent character and are in a plane orthogonal to the O–U–O bonds. Thus the uranyl group would show sexa-covalency and therefore involve the use of *f* orbitals.[8] Most of the evidence in favour of this assumption is based on the strong tendency of the uranyl group to co-ordinate molecules of water in the solid state and in solution, as shown by, *e.g.*, solubility, partition, conductometric, and thermochemical measurements.[9]

In Parts I [10] and II * it was found that also in complexes with β-diketones the uranyl group, even when bonded to two diketone radicals, appears to be co-ordinatively unsaturated and tends to co-ordinate donor molecules, *e.g.*, water, alcohols, nitrogen bases, etc. In order to get more information on the stereochemistry of the uranyl group and its co-ordinating power we investigated the infrared spectra of these, and some other complexes.

Experimental.—Preparation of complexes. Those with benzoylacetone and dibenzoylmethane were prepared as described previously.[10] Those with acetylacetone were prepared according to Biltz and Hager.[11]

The monohydrate of the dibenzoylmethane complex, *aquobis(dibenzoylmethane)uranyl*, was prepared as follows: the anhydrous complex was finely ground with hexachloro-1 : 3-butadiene, its colour changing from red-brown to orange-yellow. On evaporation of the solvent in air a yellowish-orange powder was obtained (Found: C, 48·9; H, 3·2; U, 32·4. $C_{30}H_{22}O_6U,H_2O$ requires C, 49·0; H, 3·3; U, 32·4%).

Absorption spectra. The spectra were taken with a Perkin-Elmer 21 recording spectrophotometer fitted with a rock-salt prism, and a 12C spectrophotometer fitted with a lithium fluoride prism. The samples were examined as Nujol mulls and in some cases, in the 3μ region, in mulls of fluorocarbon.

Results and Discussion.

Absorption of Uranyl.—The vibrations of the UO_2 group are characterised [4] by three frequencies, ν_2, 210 cm.$^{-1}$; ν_1, 860 cm.$^{-1}$; ν_3, 930 cm.$^{-1}$. If the UO_2 group is not linear all three frequencies should be active both in the Raman and in the infrared spectra, but if it is linear only ν_1 should be Raman-active, and ν_2 and ν_3 only infrared-active. Conn and Wu [4] examined the Raman spectrum of uranyl nitrate, chloride, and sulphate and found the frequencies ν_1 and ν_2, while in the infrared spectra of the chloride and the acetate ν_3 and ν_1 were observed; the latter was not always established with certainty because it is weak and overlaps the very intense ν_3 band. The frequency ν_2 is outside the range of observation in the infrared region. These results were interpreted as indicating the non-linearity of the UO_2 group.

[1] Fankuchen, *Phys. Rev.*, 1933, **43**, 327, 1048; *Z. Krist.*, 1935, **91**, 473; 1936, **94**, 212.
[2] Zachariasen, *Acta Cryst.*, 1948, **1**, 277, 281.
[3] Horton, *J. Amer. Chem. Soc.*, 1956, **78**, 897.
[4] Conn and Wu, *Trans. Faraday Soc.*, 1938, **34**, 1483.
[5] Lecomte and Freymann, *Bull. Soc. chim. France*, 1941, **8**, 622.
[6] Satyanarayana, *Proc. Indian Acad. Sci.*, 1942, *A*, **15**, 414.
[7] Sevcenko and Stepanov, *Zhur. eksp. teoret. Fiz.*, 1949, **19**, 1113.
[8] Glueckauf and McKay, *Nature*, 1950, **165**, 594; Irving, *Quart. Reviews*, 1951, **5**, 208; Street and Seaborg, *J. Amer. Chem. Soc.*, 1950, **72**, 2790; Connick and Hugus, jun., *ibid.*, 1952, **74**, 6012; Coulson and Lester, *J.*, 1956, 3650.
[9] Katzin and Sullivan, *J. Phys. Colloid Chem.*, 1951, **55**, 346; McKay and Mathieson, *Trans. Faraday Soc.*, 1951, **47**, 428; Glueckauf, McKay, and Mathieson, *ibid.*, p. 437; Gardner, McKay, and Warren, *ibid.*, 1952, **48**, 997; Coulter, Pitzer, and Latimer, *J. Amer. Chem. Soc.*, 1940, **62**, 2845; Kapustinskii and Baranova, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1952, 1122; McKay, *J. Inorg. Nuclear Chem.*, 1957, **4**, 375.
[10] Sacconi and Giannoni, *J.*, 1954, 2368.
[11] Biltz, *Z. anorg. Chem.*, 1904, **40**, 221; Hager, *ibid.*, 1927, **162**, 1927.

XUM

Lecomte and Freymann [5] examined the infrared spectra of about twenty uranyl salts and found always an intense band between 907 and 940 cm.$^{-1}$, and in many of these salts a weak band at about 850 cm.$^{-1}$; they therefore favoured a non-linear UO_2 group. The same conclusion was reached by Satyanarayana [6] from Raman spectroscopy. More recently, Sevcenko and Stepanov [7] examined the infrared spectra of uranyl sulphate, the potassium double sulphate, the nitrate, and the acetate. They did not always find the

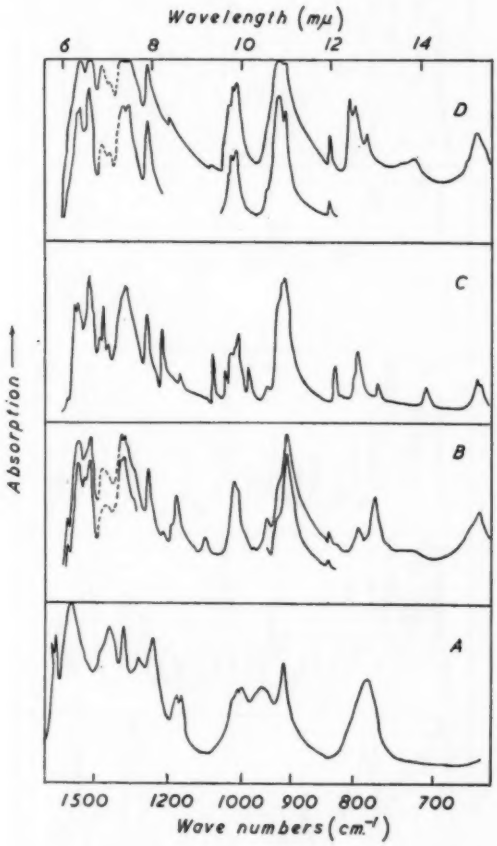


FIG. 1.* *Spectra of acetylacetone and* UO_2 *complexes*:

(*A*) Acetylacetone.
(*B*) $UO_2(acetac)_2,NH_3$.
(*C*) $UO_2(acetac)_2,C_5H_5N$.
(*D*) $UO_2(acetac)_2,H_2O$.

* In these legends, the following abbreviations are used for the diketone residues:

acetac = acetylacetone.
benzac = benzoylacetone.
dimet = dibenzoylmethane.

fundamental vibration at 860 cm.$^{-1}$, possibly owing to limitations in their apparatus, but took into account also the harmonics. They concluded that the uranyl group is probably bent in the sulphate and practically linear in the other two salts.

In short, the conclusions derived from infrared spectroscopy are ambiguous because the two bands attributed to a bent form of the uranyl group have not always been observed with certainty.

To explain the foregoing inconsistencies, Crandall [12] assumes that in solution the " co-ordinating " power of the ions surrounding the uranyl group can change the shape from linear to bent, shifting the vibration of the uncomplexed ion and breaking the selection rules for the gaseous ion. Sutton,[13] on the basis of Raman measurements, confirmed the

[12] Crandall, *J. Chem. Phys.*, 1949, **17**, 602.
[13] Sutton, *Nature*, 1952, **169**, 235.

hypothesis that in solution the linear uranyl ion is perturbed by strong fields. On the other hand, a re-examination of some old infrared and Raman spectroscopic data in the light of studies of fluorescence spectra, favours a linear structure for the uranyl radical.[14]

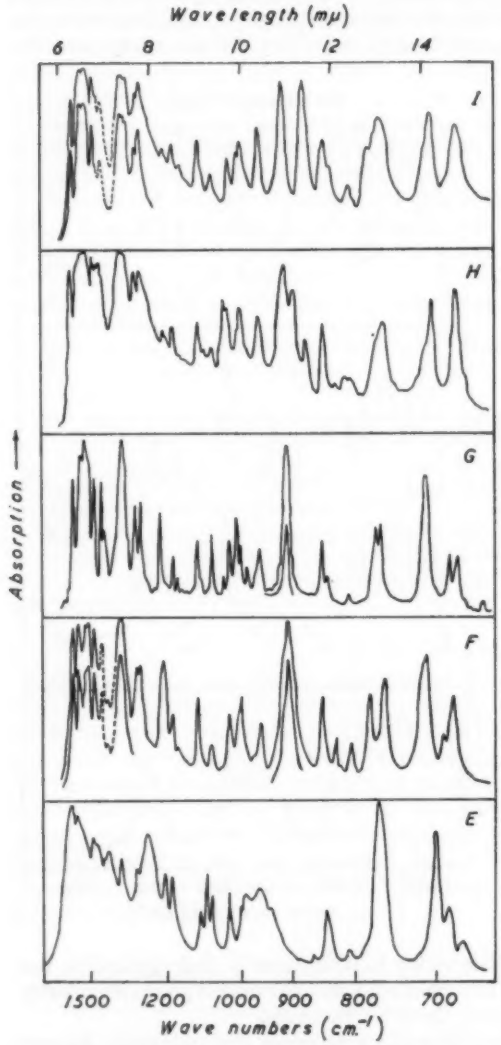


FIG. 2. *Spectra of benzoylacetone and* UO_2 *complexes:*

(*E*) Benzoylacetone.
(*F*) $UO_2(benzac)_2.NH_3$.
(*G*) $UO_2(benzac)_2.C_5H_5N$.
(*H*) $UO_2(benzac)_2.2{\cdot}5H_2O$.
(*I*) $UO_2(benzac)_2$.

Hence the problem of the structure of the uranyl radical cannot be considered to be satisfactorily solved.

The complexes here examined, containing water, ammonia, or pyridine of crystallisation, show a very strong band at about 910 cm.$^{-1}$ (Figs. 1, 2, 3) whose position is as follows:

[14] Dicke and Duncan, "Spectroscopic Properties of Uranium Compounds, National Nuclear Energy Series, Division III, Vol. 2, McGraw-Hill Book Company, Inc., New York, 1949; Seaborg and Katz, "The Actinide Elements," National Nuclear Energy Series, Division IV, Vol. 14 A, McGraw-Hill Book Company, Inc., New York, 1954, pp. 165, 319.

XUM

in the complexes of acetylacetone it is between 925 and 910 cm.$^{-1}$, in those of benzoylacetone about 910 cm.$^{-1}$, and in those of dibenzoylmethane between 913 and 900 cm.$^{-1}$. It can be attributed to ν_3. In the acetylacetone complexes a second band, of low intensity, is present in the region 830—828 cm.$^{-1}$. Comparison with the spectra of the

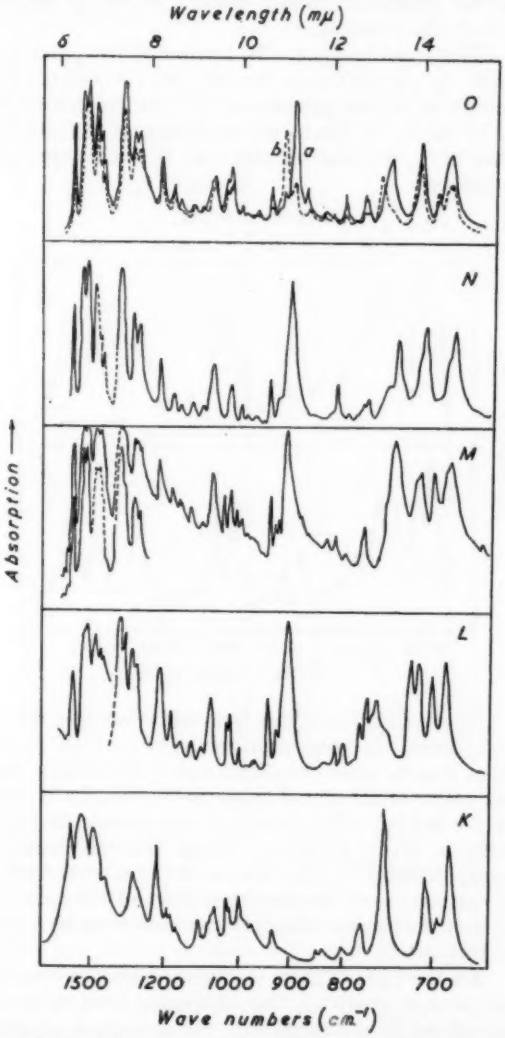


FIG. 3. *Spectra of dibenzoylmethane and UO_2 complexes*:
(*K*) Dibenzoylmethane.
(*L*) $UO_2(dimet)_2,NH_3$.
(*M*) $UO_2(dimet)_2,C_5H_5N$.
(*N*) $UO_2(dimet)_2,H_2O$.
(*O*) $UO_2(dimet)_2,2{\cdot}5H_2O$.

compounds $UO_2(OAc)_2,2H_2O$ and $UO_2(NO_3)_2,6H_2O$ (Fig. 5) showed that in the latter, in addition to the band ν_3, one can observe also a second band of very low intensity at 864 and 836 cm.$^{-1}$ which was attributed to the ν_1 vibration of the uranyl group.[4] This allows us to attribute the weak band of the acetylacetone complexes at 830—828 cm.$^{-1}$ to ν_1 vibration.

In the complexes of benzoylacetone and dibenzoylmethane the complexity of the spectra and the presence of absorption maxima of the ligands in the 860—830 cm.$^{-1}$ region do not allow us to ascertain the presence of the ν_1 band.

The anhydrous complexes with benzoylacetone and dibenzoylmethane show two bands each: at 915 and 887 cm.$^{-1}$ and at 920 and 886 cm.$^{-1}$ respectively (Figs. 2, 4). The spectra of two different samples of the latter were examined: one was obtained by double recrystallisation of the hydrate from benzene and ligroin, and the other by dehydration of the hydrated product under vacuum as described previously.[10] The spectra were practically identical.

These two bands can be attributed to ν_3 and ν_1 vibrations. It is noticeable however that: (*a*) the separation between the two frequencies, 28 and 34 cm.$^{-1}$ respectively for the complexes of benzoylacetone and dibenzoylmethane, is about half the theoretical value of 70 cm.$^{-1}$; (*b*) the theory predicts that the intensity of ν_3 should be much greater than that of ν_1, whereas we find that in our compounds both bands have practically equal intensity.

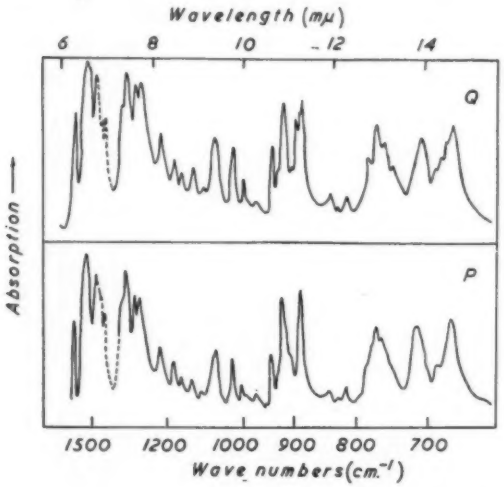
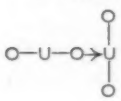


FIG. 4. *Spectra of* $UO_2(dimet)_2$:
(*P*) *Sample obtained by dehydration at* 100° in vacuo.
(*Q*) *Sample obtained by crystallisation from benzene.*

An explanation of this fact can be found in the modified crystal field of the anhydrous complexes. In these compounds, in fact, the " surroundings " of the UO_2 group differ from that in other complexes and it is probable that the aromatic groups of the ligands are nearer to the uranyl group, in the absence of molecules of water, ammonia, or pyridine in the crystal. Therefore it is conceivable that the interaction of these organic groups with the uranyl group may change the configuration or influence the polarisability of this group, altering the positions and the relative intensities of the absorption maxima and giving rise to new frequencies at 886 and 876 cm.$^{-1}$. An analogous change of the spectrum of uranyl sulphate trihydrate was observed by Sevcenko and Stepanov [7] on dehydration of this salt.*

On the basis of these results no definitive conclusions can be drawn about the form of the uranyl group in the complexes here examined. These results can probably be considered in agreement with the concept of an almost linear uranyl group disturbed by a strong local field, mainly in the case of anhydrous complexes. In the last case, however, a bent form for the uranyl radical cannot be excluded.

* The authors are grateful to a Referee for suggesting an alternative explanation for the changes occurring near 11 μ on dehydration of hydrated dibenzoylmethane and benzoylacetone complexes, and the behaviour of uranyl sulphate trihydrate on dehydration. It is suggested that the removal of co-ordinated water might allow an oxygen atom of one uranyl group to co-ordinate to the uranium atom of another uranyl group, *e.g.*, as in the inset. This would certainly alter the UO_2 frequencies and bond intensities while retaining the linear or near-linear structure of the group.



XUM

Absorption of Water.—Water vapour shows three fundamental bands: at 3756, 3652, and 1595 cm.$^{-1}$;[15] the first two correspond to stretching vibrations and the third to a bending vibration. All the hydrated complexes absorb between 3570 and 3100 cm.$^{-1}$ (see Fig. 6). This absorption is clearly due to the presence of water because the diketones and the anhydrous complexes do not absorb in this region. In some cases sharp bands are observed, while in others there is a broad ill-defined band.

FIG. 5. FIG. 6. FIG. 7.

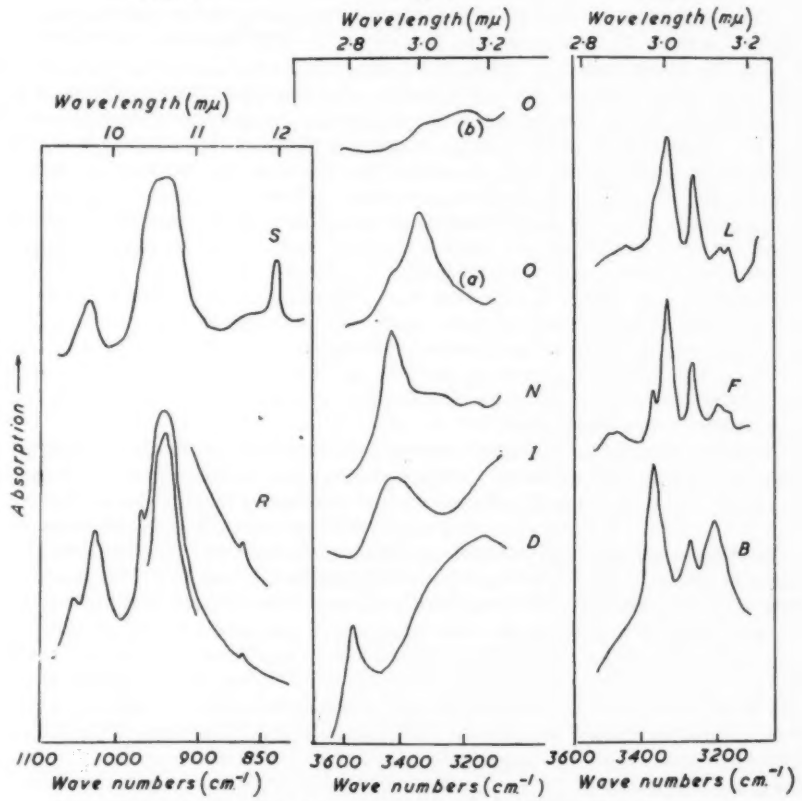


FIG. 5. *Spectra of (R) uranyl acetate and (S) uranyl nitrate.*

FIG. 6. *Spectra of hydrated uranyl–diketone complexes in the absorption region of water.*

FIG. 7. *Spectra of ammoniated uranyl–diketone complexes in the absorption region of ammonia.*

Absorption in this region is due to O–H stretching. The fact that there are no frequencies higher than 3570 cm.$^{-1}$ shows that the O–H stretching vibrations are not completely free, probably because of hydrogen bonding. The very broad band observed in many cases is an indication that, in all probability, different types of hydrogen bonding are present because of the presence of many oxygen atoms in the carbonyl groups. In some cases one observes that different samples of the same compound, from different preparations and with correct analyses, absorb differently in this region. This is so with

[15] Herzberg, "Molecular Spectra and Molecular Structure: Infrared and Raman Spectra of Polyatomic Molecules," Van Nostrand Co., New York, 1947.

curves (*a*) and (*b*) of the complex with dibenzoylmethane. The peak on the high-frequency side in curve (*a*) can be attributed to interstitial water, less strongly bound than the other water molecules.

The spectrum of water in the $2\frac{1}{2}$ hydrate of the complex of dibenzoylmethane varies even with the manipulation of the sample. The lack of reproducibility in the 3μ region is not observed in the monohydrate of the same complex. This leads to the supposition that the molecules of water in the former complex are not all bound equally strongly.

These variations of the O–H stretching band are accompanied by marked variations of the UO_2 band at about 910 cm.$^{-1}$ as shown by the spectra of two different samples (*a*) and (*b*) of the same $2\frac{1}{2}$ hydrate in Fig. 3 (curve *O*). This interaction between the UO_2 group and the water molecules leads to the conclusion that the UO_2 radical is closely bonded to at least a part of the crystal water. This supports the hypothesis of McKay and his co-workers,[9] and analogous ideas put forward in previous investigations (Parts I and II). According to these views, the uranyl group, in its inorganic salts and its complexes with β-diketones, tends to co-ordinate molecules of water. The first sphere of co-ordinated water, in turn, binds further water molecules through hydrogen bonding. Moreover, the spectroscopic data do not allow an estimate to be made of the strength of the bond between water and the central uranium atom. The presence of co-ordinate bonds between uranium and water molecules should give rise to new absorption bands corresponding to new modes of vibration (*e.g.*, rocking, etc.) of the water bonded to the central uranium atom. However, these bands are expected in the 10—14 μ region,[16] and here the presence of other strong absorption bands does not permit of their identification. Also, the 1595 cm.$^{-1}$ band of water is not identifiable owing to the complexity of the spectrum in this region, due to absorption of various functional groups such as carbonyl, phenyl, and furan rings.[17]

Absorption of Ammonia.—Gaseous ammonia shows two bands in the 3μ region: 3337 and 3450 cm.$^{-1}$. In Fig. 7 are drawn the absorption spectra, in this region, of the complexes studied by us. These curves show three main absorption maxima between 3166 and 3367 cm.$^{-1}$, *i.e.*, shifted towards lower frequencies with respect to those in gaseous ammonia. With the benzoylacetone and dibenzoylmethane complexes the first and third peaks appear to be split and shifted towards lower frequencies. These bands indicate that the nitrogen atom is co-ordinated to the uranium atom. The frequency shifts observed are of the same order of magnitude as those observed in complex ammines of the " ionic " type, *e.g.*, $[Co(NH_3)_6]Cl_2$ and $[Ni(NH_3)_6]Cl_2$, but lower than those observed in " covalent " complexes, *e.g.*, $[Co(NH_3)_6]Cl_3$ and $[Cr(NH_3)_6)Cl_3$.[18] This would lead to the conclusion that the U–N bond in these complexes is only partially covalent. A definite conclusion, however, cannot be reached because the shift toward lower frequencies in the NH_3 bands could be attributed chiefly to the presence of hydrogen bonds in the crystal.

The great complexity of the spectra does not readily allow the assignment of the many other bands observed to the functional groups present, which is, however, beyond the scope of the present investigation.

The authors thank the Italian " Consiglio Nazionale Ricerche " for support.

INSTITUTE OF GENERAL CHEMISTRY,
THE UNIVERSITY, PALERMO. [*Received, December 12th*, 1957.]

[16] Fujita, Nakamoto, and Kobayashi, *J. Amer. Chem. Soc.*, 1956, **78**, 3963.
[17] Holtzclaw, jun., and Collman, *J. Amer. Chem. Soc.*, 1957, **79**, 3318.
[18] Svatos, Curran, and Quagliano, *ibid.*, 1955, **77**, 6159.

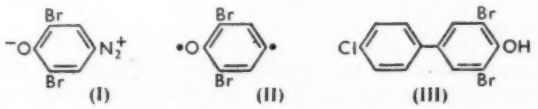
XUM

866. *A Further Study of the Thermal Decomposition of 3 : 5-Dibromobenzene 1 : 4-Diazo-oxide.*

By M. J. S. Dewar and A. N. James.

3 : 5-Dibromobenzene 1 : 4-diazo-oxide has been decomposed in a variety of aromatic solvents and the total relative rate factors for reaction of the intermediate with the solvent have been determined. The variation of these factors with solvent structure confirms the earlier deduction [1] that the intermediate is a diradical.

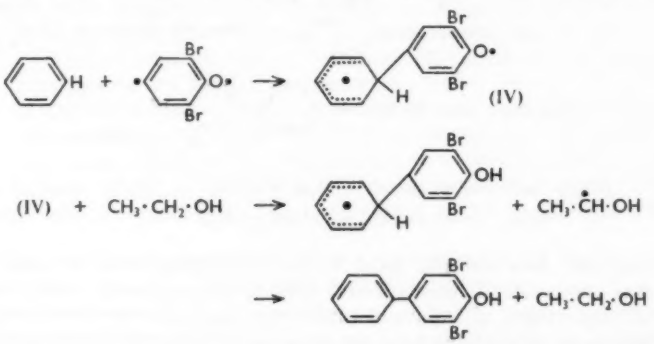
In a previous paper [1] we deduced that the first step in the decomposition of 3 : 5-dibromobenzene 1 : 4-diazo-oxide (I) in chlorobenzene was elimination of nitrogen, giving rise to the diradical (II). It was argued that the radical centre *para* to oxygen should have the same order of reactivity as that in phenyl monoradical, and the formation of polymers with molecules of solvent incorporated was ascribed to radical-substitution of the solvent through this reactive centre. We have now found that similar reactions take place in *o*- and *p*-dichlorobenzene, in bromobenzene, and in nitrobenzene, giving rise to polymers of analogous structure.



(I) (II) (III)

We also reported [1] that the decomposition of the diazo-oxide in chlorobenzene gave small amounts of diphenyl derivatives, the compound (III) being isolated in a pure state. We have now found that this type of reaction predominates in benzene, fluorobenzene, anisole, *NN*-dimethylaniline, or benzonitrile, giving rise to 3 : 5-dibromo-4-hydroxydiphenyl derivatives in fair yields.

This second mode of decomposition could be made to predominate in all cases, by adding 1% of ethanol; the ethanol probably acted as a hydrogen-transfer catalyst by the path shown in the reaction scheme. The first step of this mechanism involves radical-



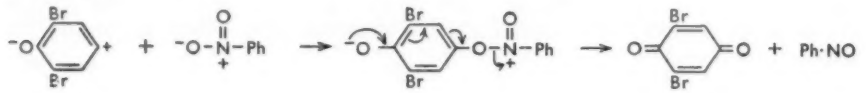
(IV)

substitution of the aromatic solvent by a substituted phenyl radical; it seemed to us that this mechanism could be confirmed by comparing the total relative rate factors for attack on different solvents with those measured by Hey and his collaborators [2] for the analogous reaction of phenyl radicals.

[1] Dewar and James, *J.*, 1958, 917.
[2] Hey *et al.*, *J.*, 1934, 1727; 1952, 1974, 2094; 1953, 44; 1954, 794, 1425, 3352; 1955, 6, 1425; 1956, 1475.

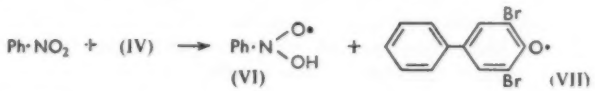
The measurements were carried out by the competitive method, using mixtures of the various substituted benzenes with benzene itself, in presence of ethanol. The reactions seemed to proceed particularly well under these conditions, the yields of mixed hydroxydiphenyls being over 85% in all but one case. The proportions of diphenyls were determined by elementary analysis.

Nitrobenzene proved exceptional. Decomposition of the diazo-oxide in a mixture of benzene and nitrobenzene gave a rather low yield of 3 : 5-dibromo-4-hydroxydiphenyl, and a polymer which appeared to consist of bromodiphenylyloxy- and dibromophenoxy-units. Neither product contained nitrogen. On the other hand nitrosobenzene was found in significant quantities, and polarography indicated the presence of 2 : 6-dibromobenzoquinone. It is possible that reaction of the diradical (II) with nitrobenzene gives rise to oxygen-abstraction rather than substitution, in contrast to the reaction of phenyl radicals which gives relatively good yields of nitrodiphenyls; the diradical (II) could be in rapid equilibrium with the zwitterionic isomer (V) which might be expected to react as follows:

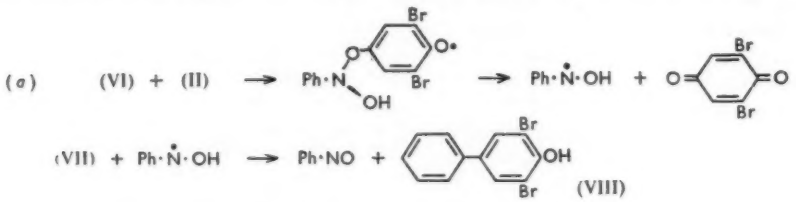


(V)

However, in pure nitrobenzene the diradical (II) gave polymers containing nitrogen, and it seems more reasonable to suppose that, in the competitive experiment with benzene, nitrobenzene abstracted hydrogen from the intermediate (IV) in the following manner:



The intermediate (VI) might then react in a number of ways to give the observed products:



(b) (VI) + (IV) → Ph·NO + H_2O + (VIII)

(c) 2(VI) → $Ph·NO_2$ + Ph·NO + H_2O

Decalin and the diradical (II) gave 2 : 6-dibromophenol and a copolymer which apparently was composed of decalinyl and dibromophenoxy-units, while carbon tetrachloride gave copolymers of bromochlorophenoxy- and dibromophenoxy-units. Both these reactions might be expected from the diradical, which could abstract hydrogen and chlorine respectively from the two solvents.

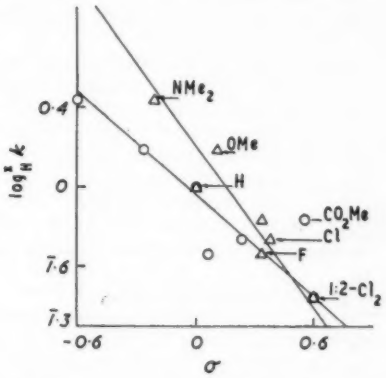
Table 1 gives the total relative rate factors for reaction of the diazo-oxide (I) with various benzene derivatives, and the total relative rate factors reported by Hey and his collaborators [2] for the similar reactions of phenyl radicals. In both cases the spread of rates is small, as would be expected for radical reactions; this parallel confirms the view [1] that the intermediate from 3 : 5-dibromobenzene-1 : 4-diazo-oxide reacts as a diradical under these conditions.

It is also clear that the diradical (II) shows significant electrophilic character, just as do the relatively electronegative radicals derived from chlorobenzoyl and nitrobenzoyl peroxide.[3] This is also indicated in the Figure which shows Hammett plots of the total

TABLE 1. *Total relative rate factors for reaction of diradical* (I) *and phenyl radicals with various benzene derivatives.*

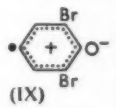
Solvent	$^{X}_{H}k$(I)	$^{X}_{H}k$(Phenyl)	Solvent	$^{X}_{H}k$(I)	$^{X}_{H}k$(Phenyl)
NN-Dimethylaniline ...	2·8	—	Me benzoate	0·78	—
Pyridine	2·6	1·04	Chlorobenzene	0·54	1·44
Anisole	1·6	2·50	*o*-Dichlorobenzene	0·28	—
Fluorobenzene	0·46	1·35			

relative rate factors for the diazo-oxide (I) against σ-constants for the substituents. Since the orientations of the products are not known, plots are shown for *meta* and *para* σ-constants. These suggest that methyl benzoate is probably *meta*-substituted largely, in accordance with the apparently marked electrophilic nature of the diradical (II).



Plots of $\log {}^{X}_{H}k$ *against* σ *for* para- (○) *and* meta-*substitution* (△).

This electrophilic character can be ascribed to a polarisation of the π-electrons by the electronegative oxygen atom, the structure approximating to (IX).



(IX)

Further evidence for the electrophilic nature of the diazo-oxide (I) is provided by the partial rate factors for *ortho-*, *meta-*, and *para*-substitution in chlorobenzene. The proportions of isomers in the diphenyl fraction were determined by ultraviolet spectrophotometry,[4] and the partial rate factors were then calculated by using the known overall reactivity of chlorobenzene relative to benzene (Table 1). Table 2 shows the partial rate factors for reaction of chlorobenzene with the diazo-oxide (I), with phenyl radicals, and with acetyl nitrate.[5]

TABLE 2. *Partial rate factors for reaction of chlorobenzene with the diazo-oxide* (I), *phenyl radicals, and acetyl nitrate.*

Reagent	$^{Cl}_{H}k_o$	$^{C}_{H}k_m$	$^{Cl}_{H}k_p$
(I)	0·162	0	0·216
Phenyl	2·60	1·12	1·19
Acetyl nitrate	0·03	0	0·139

It will be seen that the pattern of partial rate factors for the diazo-oxide (I) resembles that for an electrophilic reaction (nitration) rather than that for reaction with phenyl radicals.

[3] Augood and Williams, *Chem. Rev.*, 1957, **57**, 123.
[4] Dewar and Urch, *J.*, 1957, 345.
[5] Ingold *et al.*, *J.*, 1938, 905, 918.

XUM

Experimental

Materials.—**3** : 5-Dibromobenzene-**1** : **4**-diazo-oxide was prepared in quantities of about 10 g. by Böhmer's procedure [6] and dried in a vacuum over phosphoric oxide for 2 days. The compound should be handled carefully and in small quantities since it is dangerously explosive; in an earlier investigation considerable damage was caused by the detonation of 70 g. of the material on gentle rubbing. Chlorobenzene was washed with concentrated sulphuric acid and water, dried ($CaCl_2$), and fractionated from phosphoric oxide. *o*-Dichlorobenzene and fluorobenzene were fractionated from phosphoric oxide. Bromobenzene was fractionated under reduced pressure from phosphoric oxide. Nitrobenzene was distilled and then purified by partial freezing. *NN*-Dimethylaniline (" AnalaR ") and *p*-dichlorobenzene (" purified " grade) were redistilled. Benzonitrile was washed with aqueous potassium carbonate, dried ($CaCl_2$; P_2O_5), and distilled. Anisole was dried ($CaCl_2$), then distilled in a vacuum. Decalin was washed with dilute sulphuric acid, aqueous alkali, and water. After drying ($CaSO_4$) it was fractionated under reduced pressure. Carbon tetrachloride was boiled under reflux with 5% sodium hydroxide solution, washed with water, dried ($CaCl_2$), and distilled. Pyridine, after several days over potassium hydroxide, was distilled from fresh potassium hydroxide. Methyl benzoate was prepared in the usual way from " AnalaR " benzoic acid, dried ($CaCl_2$), and distilled. Ethanol was dried with magnesium and distilled. Benzene (crystallisable grade) was dried (Na wire) and distilled.

Decompositions in Pure Solvents.—These were carried out by heating weighed portions (2—4 g.) of diazo-oxide (I) in pure solvents (250 c.c.) at 80° (thermostat) with stirring.

The diazo-oxide (3·00 g., 0·0108 mole) in *o*-dichlorobenzene gave in 2 hr. much tar and polymer (0·9 g.) [Found: C, 47·0; H, 2·2; Br, 25·2; Cl, 23·8. Calc. for $(C_{12}H_5OCl_2Br)_n$: C, 45·6; H, 1·6; Br, 25·3; Cl, 22·5%].

The diazo-oxide (2·95 g.) in *p*-dichlorobenzene gave in 2 hr. a little tar and polymer (1·3 g.) (Found: C, 46·3; H, 2·0; Br, 30·5; Cl, 13·6. Calc. for copolymer of $C_{12}H_5OClBr$ (85%) and $C_6H_2OBr_2$ (15%): C, 43·6; H, 1·6; Br, 30·1; Cl, 15·2%).

The diazo-oxide (1·80 g.) in bromobenzene gave polymer (0·95 g.) [Found: C, 44·9; H, 2·3; Br, 48·2. Calc. for $(C_{12}H_6OBr)_n$: C, 44·2; H, 1·8; Br, 49·9%]. Some tar (0·25 g.) and phenolic material (0·35 g.) were also formed.

The diazo-oxide (2·85 g.) in nitrobenzene gave in 2 hr. polymer (0·6 g.) (Found: C, 41·4; H, 2·2; O, 11·4; N, 1·8. Calc. for 1 : 1 copolymer of $C_{12}H_6O_3NBr$ and $C_6H_2OBr_2$: C, 40·0; H, 1·6; O, 11·8; N, 2·5%). There were also isolated tarry phenols (1·20 g.) from which 2 : 4 : 6-tribromophenol (0·2 g.) was obtained by steam-distillation and converted into the methyl ether, m. p. and mixed m. p. 86°.

The diazo-oxide (0·85 g.) in fluorobenzene gave in 1 hr. a crystalline phenol (0·9 g., 70%). Repeated recrystallisation from light petroleum (b. p. 60—80°)–chloroform gave **3** : 5-*dibromo*-**4**′-*fluoro*-**4**-*hydroxydiphenyl* as needles, m. p. 150—151° (Found: C, 41·7; H, 2·0. $C_{12}H_7OBr_2F$ requires C, 41·7; H, 2·3%). 4-Fluoro-4′-hydroxydiphenyl, prepared from the amino-compound by the method employed for 4-chloro-4′-hydroxydiphenyl, crystallised from chloroform in needles, m. p. 167—168° (lit.,[7] m. p. 167—168°); it (0·4 g.) was converted into the above dibromo-derivative by bromine (0·68 g.) in carbon disulphide (10 c.c.), and this crystallised as above in needles, m. p. and mixed m. p. 150—151°. The monomethyl ether crystallised from light petroleum (b. p. 40°) in needles, m. p. 107—108°.

The diazo-oxide (2·25 g.) in *NN*-dimethylaniline gave in 2 hr. a deep red solution which was extracted with 5N-sodium hydroxide. The alkaline extract on acidification (pH 5·0) deposited a dark phenolic mixture (2·0 g., 70%). This mixture was methylated (diazomethane) and the product converted into its picrate (impure), needles, m. p. 191—192° (decomp.) (from alcohol) (Found: C, 41·0; H, 2·9; N, 9·1; Br, 26·0. Calc. for $C_{15}H_{15}ONBr_2,C_6H_2ON_3$: C, 41·0; H, 3·1; N, 9·0; Br, 24·0%). The base, liberated by concentrated aqueous ammonia, crystallised from alcohol in rosettes (still impure), m. p. 71—72° (Found: C, 46·5; H, 4·0; N, 3·6; Br, 42·3. Calc. for $C_{15}H_{15}ONBr_2$: C, 46·7; H, 3·9; N, 3·6; Br, 41·6%).

The diazo-oxide (2·90 g.) in benzonitrile gave in 2 hr. a mixture of phenols (2·8 g., 80%) from which two isomers, **3** : 5-*dibromo*-**x**′-*cyano*-**4**-*hydroxydiphenyl*, were obtained. One crystallised from benzene in needles, m. p. 230—231° (Found: C, 44·7; H, 2·2; N, 3·9; Br, 45·2;

[6] Bohmer, *J. prakt. Chem.*, 1881, **24**, 453.
[7] Fleishman and Roe, *J. Amer. Chem. Soc.*, 1947, **69**, 509.

$C_{13}H_7ONBr_2$ requires C, 44·2; H, 2·2; N, 3·9; Br, 45·2%), the other from alcohol in needles, m. p. 182—184° (Found: C, 43·9; H, 2·2; N, 4·0; Br, 44·9%).

The diazo-oxide (2·85 g.) in anisole gave in 3 hr. a mixture of phenols (3·45 g., 95%) from which 3 : 5-dibromo-4-hydroxy-4′-methoxydiphenyl was obtained by repeated recrystallisation from light petroleum (b. p. 60—80°) as pale brown needles, m. p. 128—129° (Found: C, 43·8; H, 3·1; Br, 43·6; OMe, 8·6. Calc. for $C_{13}H_{10}O_2Br_2$: C, 43·6; H, 2·8; Br, 44·46; OMe, 8·7%). Boiling the product (0·7 g.) with hydriodic acid in acetic acid gave the diphenyl (0·1 g.), m. p. 272—274° (from benzene) (lit.,[8] m. p. 274—275°).

The diazo-oxide (2·25 g.) in decalin gave in 24 hr. 2 : 6-dibromophenol (0·75 g.) which crystallised from hot water in needles, m. p. and mixed m. p. 55—56°. Polymer (0·5 g.) was also obtained [Found: C, 59·5; H, 5·7; Br, 27·7. Calc. for a copolymer of $C_{10}H_{16}$ (66%) and $C_6H_2OBr_2$ (34%): C, 59·4; H, 6·4; Br, 31·1%].

The diazo-oxide (2·10 g.) in carbon tetrachloride gave in 18 hr. a red solution from which was obtained a polymer (0·35 g.) (Found: C, 31·9; H, 1·4; Br, 51·1; Cl, 9·8. Calc. for a 1 : 1 copolymer of $C_6H_2OBr_2$ and C_6H_2OClBr: C, 31·6; H, 0·9; Br, 52·6; Cl, 7·8%). There was also obtained an ether-soluble solid (1·1 g.) which did not crystallise.

Competitive Experiments.—These were carried out by heating the diazo-oxide (about 3 g.) in an equimolecular mixture of benzene and a second solvent containing ethanol (1% v/v) at 80° (thermostat) with stirring. The phenolic product was then extracted with aqueous sodium hydroxide, weighed, and in several cases methylated (diazomethane). The ethers were purified by passage in benzene down a column of alumina with about 5% loss of product. Independent experiments showed that the recovery of the ethers was almost quantitative.

Chlorobenzene. The diazo-oxide (2·75 g.) was decomposed in 5 hr. to a phenolic mixture (2·80 g., 87%), methylation of which (1·05 g.) gave pale yellow crystals (1·10 g.) [Found: C, 44·0; H, 2·7; Br, 45·0; Cl, 3·4. Calc. for $C_{13}H_9OClBr_2$ (36%) and $C_{13}H_{10}OBr_2$ (64%): C, 44·0; H, 2·9; Br, 44·8; Cl, 3·6%].

o-*Dichlorobenzene.* The diazo-oxide (3·00 g.) was decomposed in 4½ hr. to an orange-brown phenolic mixture (3·35 g., 95%), which (1·35 g.) gave a pale-orange crystalline methyl ether (1·25 g.) [Found: C, 43·7; H, 2·9; Br, 42·9; Cl, 4·4. Calc. for $C_{13}H_8OCl_2Br_2$ (22%) and $C_{13}H_{10}OBr_2$ (78%): C, 43·7; H, 2·7; Br, 44·8; Cl, 4·4%].

Fluorobenzene. The diazo-oxide (3·00 g.) was decomposed in 6 hr. to almost white, crystalline phenols (3·25 g., 86%) which yielded on methylation a crystalline mixture of methyl ethers (3·15 g.) [Found: C, 44·4; H, 2·6; Br, 46·9; F, 1·7. Calc. for $C_{13}H_9OBr_2F$ (31·4%) and $C_{13}H_{10}OBr_2$ (68·5%): C, 44·8; H, 2·8; Br, 46·1; F, 1·7%].

Anisole. The diazo-oxide (2·00 g.) was decomposed in 4½ hr. to a pale yellow crystalline phenolic mixture (2·30 g., 93%), which (0·75 g.) was methylated to a pale yellow oil (0·75 g.) [Found: C, 45·0; H, 3·4; Br, 43·9; OMe, 13·9. Calc. for $C_{14}H_{12}O_2Br_2$ (39%) and $C_{13}H_{10}OBr_2$ (61%): C, 45·3; H, 3·1; Br, 44·4; OMe, 13·8%].

NN-*Dimethylaniline.* The diazo-oxide (2·95 g.) decomposed in 2 hr., giving a deep red solution which on extraction with alkali and acidification (pH 5) deposited a dark brown crystalline phenolic mixture (3·15 g., 87%). Methylation of this (0·85 g.) gave a brown liquid (0·80 g.) [Found: C, 42·8; H, 3·2; N, 2·2; Br, 47·7. Calc. for $C_{15}H_{15}ONBr_2$ (61%), $C_{13}H_{10}OBr_2$ (22%), and $C_7H_5OBr_3$ (17%): C, 43·0; H, 3·3; N, 2·3; Br, 47·0%].

Pyridine. The diazo-oxide (2·1 g.) gave in 1½ hr. a very dark red solution. After removal of the rest of the solvent under reduced pressure, the black residue was dissolved in ether and extracted with alkali, giving a dark phenolic mixture (2·30 g., 86%), methylated to a brown liquid (2·15 g.) [Found: C, 43·1; H, 3·1; N, 2·9; Br. 47·4. Calc. for $C_{12}H_9ONBr_2$ (72%) and $C_{13}H_{10}OBr_2$ (28%): C, 43·0; H, 2·8; N, 2·9; Br, 47·1%].

Methyl benzoate. The diazo-oxide (3·00 g.) was decomposed in 5 hr. to a dark red solution from which a crystalline phenolic mixture (3·80 g., 95%) was isolated and converted into mixed methyl ethers (3·65 g.) [Found: C, 43·4; H, 2·9; Br, 45·0. Calc. for $C_{14}H_{10}O_3Br$ (44%) and $C_{13}H_{10}OBr$ (56%): C, 44·4; H, 2·7; Br, 44·5%]. The product (1·533 g.) with alcoholic 0·5N-potassium hydroxide gave a non-acidic component (0·806 g., 56%) which on one recrystallisation from light petroleum (b. p. 60—80°) yielded pale brown needles of 3 : 5-dibromo-4-hydroxydiphenyl, m. p. and mixed m. p. 95—96°. The acidic component (0·755 g., 44%) was dissolved in alcohol and titrated to phenolphthalein (Found: equiv., 393. Calc. for $C_{14}H_{10}O_3Br_2$: equiv., 386).

[8] Hirsh, *Ber.*, 1889, **22**, 235.

Nitrobenzene. The diazo-oxide (3·00 g.) decomposed in 5 hr., giving a dark red solution, from which a phenolic mixture (0·95 g., 27%) was obtained (Found: C, 43·6; H, 3·0; Br, 47·7. Calc. for $C_{12}H_8OBr_2$: C, 42·2; H, 2·5; Br, 48·6%). The extracted solution was dried ($CaCl_2$) and distilled under reduced pressure. When the nitrobenzene began to distil (~120°/14 mm.) the distillate became green. This distillate was compared spectroscopically with a solution of nitrosobenzene in nitrobenzene (413 mg./l.) and shown to have an identical band at 745 mμ. After the solution had been evaporated to about 5 c.c. it was poured into stirred methanol, to yield an orange polymer (1·25 g., 50%) [Found: C, 51·3; H, 3·5; Br, 38·1. Calc. for $C_6H_2OBr_2$ (20%) and $C_{12}H_7OBr$ (80%): C, 52·2; H, 2·4; Br, 38·7%]. The filtrate after removal of polymer and phenolic products was concentrated under reduced pressure to about 2 c.c. A filtered solution of this residue (0·85 g.) in alcohol (50 c.c.) and phosphate buffer (50 c.c.) (final pH 7·45) was examined polarographically. It showed a half-wave at −0·05v with reference to a calomel electrode. The wave was slightly masked by condenser current. However, variation of the concentration of the solution showed this half-wave to be characteristic. Similar behaviour was shown by solutions of 2 : 6-dibromobenzoquinone. The half-wave potentials obtained for solutions of 2×10^{-4}, 5×10^{-4}, and 2×10^{-3} mole/l. were −0·04, −0·07, and −0·12 v respectively.

Partial Rate Factors for Chlorobenzene.—Decomposition of the diazo-oxide (3·00 g.) in chlorobenzene (250 c.c.) containing ethanol (2·5 c.c.) in 3 hr. gave a phenolic fraction (3·90 g., 96%) which was methylated to a pale yellow oily mixture of isomeric 3 : 5-dibromo-*x*′-chloromethoxydiphenyls (3·85 g.). It was analysed spectrophotometrically by the method of Dewar and Urch [4] (Found: 2′, 60·0%; 4′, 40·0%). The preparation of the necessary reference compounds is described below. All spectra were measured with a Unicam S.P. 1500 spectrophotometer. The 2′ : 4′ ratio is unlikely to be in error by more than 1%.

3 : 5-*Dibromo*-4′-*chloro*-4-*methoxydiphenyl.*—The following procedure gives a better yield than our previous method.[1] 4-Chloro-4′-nitrodiphenyl [9] crystallised from acetic acid in yellow needles, m. p. 141·5—142·5°, not altered by repeated recrystallisation (Found: C, 61·4; H, 3·5; N, 7·65; Cl, 15·0. Calc. for $C_{12}H_8O_2NCl$: C, 61·1; H, 3·4; N, 7·65; Cl, 15·2%). Turner and Le Fèvre [9] report the substance as forming almost colourless needles, m. p. 157—158°. Reduction of the nitro-compound with hydrazine hydrate in boiling absolute alcohol over a platinum–carbon catalyst gave 4-amino-4′-chlorodiphenyl (80%), crystallising from alcohol in plates, m. p. 132—133° (lit.,[10] 134°). The amine (2·0 g.) in glacial acetic acid (25 c.c.) was diazotised with sodium nitrite (0·7 g.) in concentrated sulphuric acid (6 c.c.) at 15—20°. The solution was poured on ice, then heated 1 hr. on a steam-bath; when cold, the 4-chloro-4′-hydroxydiphenyl was collected and crystallised from light petroleum (b. p. 60—80°) in pale brown needles (0·9 g.), m. p. 143—144° (lit.,[11] 146—147°). From this, 3 : 5-dibromo-4′-chloro-4-methoxydiphenyl was prepared by the method previously described.[1]

3 : 5-*Dibromo*-3′-*chloro*-4-*methoxydiphenyl.*—3-Chloro-4′-methoxydiphenyl was prepared by an Ullmann condensation of *p*-iodoanisole [12] (79·5 g.) with *m*-chloroiodobenzene [13] (78·0 g.) and copper bronze (60 g.) at 260°. The reaction was sudden and violent. Cooling and extraction with ether gave a brown oil which slowly deposited much crystalline material. This was shown to be 4 : 4′-dimethoxydiphenyl by recrystallisation from alcohol (m. p. 172°; lit.,[14] m. p. 173°). The filtrate on evaporation gave a brown oil (38 g.) which was fractionally distilled in a vacuum. The fraction (16·0 g.) of b. p. 141—145°/0·8 mm. crystallised. Three recrystallisations from alcohol yielded 3-*chloro*-4′-*methoxydiphenyl*, needles (3·1 g.), m. p. 52—53° (Found: C, 70·9; H, 4·1; Cl, 15·7; OMe, 13·7. $C_{13}H_{11}OCl$ requires C, 71·3; H, 5·0; Cl, 16·2; OCH_3, 14·1%). This product (1·8 g.) on demethylation with hydrobromic acid in acetic acid followed by recrystallisation from light petroleum (b. p. 60—80°)–chloroform gave 3-*chloro*-4′-*hydroxydiphenyl* (1·2 g.), plates, m. p. 98·5—99·5°. Treatment of this compound with bromine (2 g.) with a trace of iron powder in carbon disulphide (20 c.c.) at room temperature for 2 days gave 3 : 5-dibromo-3′-chloro-4-hydroxydiphenyl, which after repeated recrystallisation from light petroleum (b. p. 60—80°) formed needles, m. p. 122—123°. Methylation (diazomethane) and repeated recrystallisation from alcohol gave the *methyl ether* (0·2 g.) as plates,

[9] Le Fèvre and Turner, *J.*, 1928, 253.
[10] Gelmo, *Ber.*, 1906, **39**, 4176.
[11] Angeletti and Gatti, *Gazzetta*, 1928, **58**, 633.
[12] Reverdin, *Ber.*, 1896, **29**, 4176.
[13] Klages and Liecker, *J. prakt. Chem.*, 1918, **61**, 321.
[14] Ullmann and Lowenthal, *Annalen*, 1904, **332**, 67.

XUM

m. p. 134·5—135·5° (Found: C, 40·6; H, 3·1; Br, 41·3; Cl, 9·7. $C_{13}H_9OBr_2Cl$ requires C, 41·5; H, 3·1; Br, 42·5; Cl, 9·4%).

3 : 5-*Dibromo*-2′-*chloro*-4-*methoxydiphenyl*.—This was prepared by the method described previously.[1]

QUEEN MARY COLLEGE,
MILE END ROAD, LONDON, E.1.

[*Received, March 24th*, 1958.]

867. *Strength of Chloro-substituted Phenoxyacetic and Related Phosphorus-containing Acids.*

By J. N. PHILLIPS

Dissociation constants are reported for a number of chloro-substituted phenoxyacetic and phosphorus-containing analogues. Generally chloro-substitution increases acidic strength except with 2 : 6-disubstituted derivatives, whose anomalous behaviour is attributed to steric hindrance. Contrary to predicted statistical and inductive effects, both phosphinic acids and ethyl phosphonates are stronger than the corresponding phosphonic acids. The relative strength of the acid types studied is in the order phenyl dihydrogen phosphates > ethyl hydrogen (phenoxymethyl)phosphonates > phenoxymethylphosphinic acids > phenoxymethylphosphonic acids > phenoxyethyl dihydrogen phosphates > phenoxyacetic acids.

CHLORINATED phenoxyacetic acids and related compounds are of interest because of their effect on plant growth.[1] However, no systematic investigation of their acidic strength has been reported, although such data may be required for the study of their mode of action and in correlations of biological activity and chemical structure. The dissociation constants reported here refer to a number of chloro-substituted phenoxyacetic acids $Ph{\cdot}O{\cdot}CH_2{\cdot}CO_2H$, phenoxymethylphosphonic acids $Ph{\cdot}O{\cdot}CH_2{\cdot}P(:O)(OH)_2$ and their ethyl half-esters, phenoxymethylphosphinic acids $Ph{\cdot}O{\cdot}CH_2{\cdot}PH(:O)OH$, phenoxyethyl dihydrogen phosphates $Ph\,O{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}P(:O)(OH)_2$, and phenyl dihydrogen phosphates $Ph{\cdot}O{\cdot}P(:O)(OH)_2$. The growth-regulating and toxic properties of some of the phosphorus-containing acids have been reported elsewhere.[2]

EXPERIMENTAL

The applicability of potentiometric titration to the determination of dissociation constants is limited here by the poor solubility in water of di- and tri-chlorophenoxyacetic acids and by the strongly acidic nature of the first dissociating group of phosphorus-containing acids. It has however been used to determine the relative strength of the chlorophenoxyacetic acid series in 50% (w/v) ethanol and of some of its more soluble members in water. It has also been used to determine second dissociation constants in water of the phenoxymethylphosphonic acids, and of the phenoxyethyl and phenyl dihydrogen phosphates. 25 ml. of 0·01M-acid in the appropriate solvent were titrated with 0·05M-sodium hydroxide (carbonate free). The solution was maintained at 20° and was magnetically stirred throughout the titration. The pH was determined with a standard Cambridge pH-meter. Agreement between theoretical and experimental end points was within 2%. In some instances the compound was supplied as its sodium salt, in which case a back titration was carried out with standardised hydrochloric acid, and the theoretical end point assumed.

For a monobasic acid the apparent dissociation constant (K') was calculated from a number of points on each titration curve from the relation

$$pK' = pH - \log (\alpha c + [H^+])/\{(1 - \alpha)c - [H^+]\} \quad . \quad . \quad . \quad . \quad (1)$$

where α is the degree of neutralisation of the weak acid and c its total concentration. For a

[1] Leaper and Bishop, *Bot. Gazette*, 1951, **112**, 250.
[2] Greenham, *Austral. J. Sci.*, 1953, **16**, 66; *Austral. J. Biol. Sci.*, 1957, **10**, 180.

XUM

dibasic acid pK'_1 and pK'_2 were determined by applying eqn. (1) to each of the two ionisation steps.

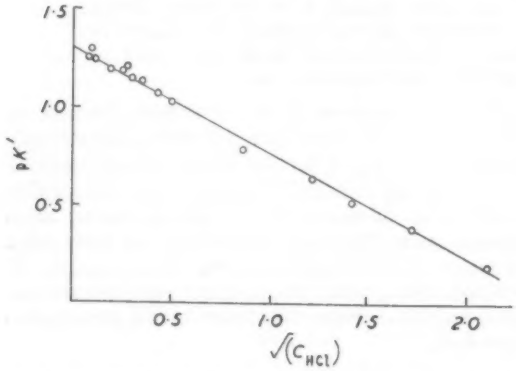
A more promising technique for aqueous solution is spectroscopic titration. There is a shift [3] in the ultraviolet spectra associated with the ionisation of aryloxyalkyl-substituted acids so that dissociation constants can be determined from the effect of pH on the spectra at concentrations considerably less than those necessary for potentiometric titration. Spectrophotometry has the further advantage of being equally applicable to weak or strong acids, whilst potentiometry is effectively limited to the former because of the high concentrations necessary to avoid corrections for hydrolysis. The optical density–pH relationship was measured at a number of wavelengths selected to give the maximum change between the two species in a Beckman spectrophotometer at 20°. The concentration of the solution (usually 5×10^{-4}M) was chosen so that Beer's law was obeyed.

pK' values were calculated from the relation

$$pK' = pH - \log[(\varepsilon_{pH}^{\lambda} - \varepsilon_1^{\lambda})/(\varepsilon_2^{\lambda} - \varepsilon_{pH}^{\lambda})] \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where ε_1^{λ} and ε_2^{λ} refer to the molar extinction coefficient for the undissociated acid and the ionic species respectively at wavelength λ and $\varepsilon_{pH}^{\lambda}$ refers to the molar extinction coefficient at wavelength λ for an intermediate pH.

The maximum change between the undissociated and the ionised form generally occurred in



Plot of pK' against $\sqrt{(C_{HCl})}$ for the first dissociation constant (K'_1) of 2 : 4-dichlorophenoxymethylphosphonic acid.

the far ultraviolet region where, because of the relatively steep slope of the ε–λ curve, a small displacement of the spectrum gave rise to a large change in absorption at a given wavelength. Because of this it was undesirable to use only one wavelength, and we normally determined the optical density–pH curve for 4 wavelengths separated by 10 Å intervals and calculated an average pK for each wavelength from a number of points on it, the mean value for the 4 wavelengths being accepted as the pK'. pK values calculated at the various wavelengths and from the different points at the one wavelength usually agreed to within $\pm 0{\cdot}05$ pK unit.

The pH of the solutions was adjusted by means of 0·01M-phosphate buffer in the region 5—8 and otherwise with hydrochloric acid solutions. pH values above 2 were determined with a glass electrode and Cambridge pH meter.

For phosphorus-containing acids the effective pH values were calculated from the known activities [4] of the various hydrochloric acid solutions used, by replacing pH by $-\log_{10}\sqrt{(a_{HCl})}$. When such values were substituted into eqn. (2), however, the calculated pK' varied with degree of ionisation, as would be expected owing to the variation in ionic strength with hydrochloric acid concentration.

This difficulty was overcome by determining the H_- acidity function [5] for hydrochloric acid solutions under these conditions so that thermodynamic $pK°$ values could be determined. 2 : 4-Dichlorophenoxymethylphosphonic acid was chosen as the standard. The optical density

[3] Phillips, *Austral. J. Chem.*, in the press.
[4] Harned and Owen, "Physical Chemistry of Electrolyte Solutions," Reinhold Publishing Corporation, New York, 1943, pp. 547, 577.
[5] Paul and Long, *Chem. Rev.*, 1956, **56**, 1.

was measured as a function of hydrochloric acid concentration (C_{HCl}) and the apparent pK' determined from a number of points on the curve by substituting $-\log_{10}\sqrt{(a_{HCl})}$ for pH in eqn. (2). A plot of pK' against $\sqrt{(C_{HCl})}$ (Figure) is straight, with slope 0·53, surprisingly close to the theoretical Debye–Hückel slope (0·50), and intercept 1·30 ± 0·05, corresponding to the thermodynamic p$K°$ value. The H_- acidity function was calculated for a particular hydrochloric acid concentration from the relation

$$H_- = -\log_{10}\sqrt{(a_{HCl})} + pK° - pK' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The usefulness of the H_- function is illustrated in Table 1 which summarises the pK values calculated as a function of degree of ionisation for 2 : 4-dichlorophenyl dihydrogen phosphate. Whereas p$K°$ calculated from H_- is constant, pK' calculated by putting pH = $-\log_{10}\sqrt{(a_{HCl})}$ varies with the degree of ionisation.

TABLE 1. *2 : 4-Dichlorophenyl dihydrogen phosphate at* 20°.

C_{HCl} (mole/l.)	7·5	6·0	4·5	1·5	0·375	0·225	0·150	0·075
α *	0·12	0·17	0·23	0·42	0·64	0·70	0·77	0·84
$-\log_{10}\sqrt{(a_{HCl})}$	−1·59	−1·31	−0·97	−0·14	+0·53	+0·76	+0·92	+1·22
pK'	−0·73	−0·62	−0·45	0	+0·28	+0·39	+0·40	+0·50
H_-	−0·16	−0·01	+0·14	+0·53	+0·85	+1·00	+1·13	+1·36
p$K°$	+0·70	+0·68	+0·66	+0·67	+0·60	+0·63	+0·61	+0·64

* α calculated for λ = 2350 Å.

TABLE 2.

Compound	pK' (H_2O), 20° Pot. I ~0·005 *	Spectr. I ~0·001 *	λ_{mean} † (Å)	pK' (H_2O), 20° Lit. values	pK' (50% ethanol), 20° Pot. I ~0·005 *	ΔpK'	Source ‡
Phenoxyacetic acid	3·11	3·12	2260	3·12 [a]; 3·17 [b]	4·30	1·18	
2-Cl- ,,	2·96	2·96	2300	2·99 [a]; 3·06 [b]	4·23	1·27	
3-Cl- ,,	2·97	2·97	2310	3·07 [b]	4·14	1·17	
4-Cl- ,,	2·99	3·00	2370	3·02 [a]; 3·10 [b]; 3·01	4·15	1·15	
2 : 4-Cl_2- ,,	—	2·86	2390	3·27 [d]; 2·81 [e]; 2·96 [f]; 3·00 [g]; 2·90 [e]; 2·64 [h]	4·10	1·24	
2 : 5-Cl_2- ,,	—	2·94	2500	—	4·13	1·19	
2 : 6-Cl_2- ,,	—	3·30	2300	—	4·22	0·92	*A*
3 : 4-Cl_2- ,,	—	2·92	2400	—	4·10	1·18	
2 : 3 : 4-Cl_3 ,,	—	2·60	2340	—	3·92	1·32	*A*
2 : 3 : 6-Cl_3 ,,	—	§	—	—	4·10	—	*A*
2 : 4 : 5-Cl_3 ,,	—	2·85	2450	2·58 [e]; 2·84 [e]	4·01	1·16	*B*
2 : 4 : 6-Cl_3 ,,	—	§	—	—	4·20	—	
α-(2 : 4-Cl_2-phenoxy)-propionic acid	—	2·86	2410	—	4·30	1·44	
β-(2 : 4-Cl_2-phenoxy)-propionic acid	—	4·42	2410	—	5·50	1·08	*C*
γ-(2 : 4-Cl_2-phenoxy)-butyric acid	—	§	—	—	5·89	—	*D*

* Mean ionic strength at half-neutralisation point.

† Mean of wavelength region from which pK values were calculated.

‡ *A*, Supplied by Timbrol Ltd., Sydney. *B*, Supplied by Dr. M. H. Maguire, Sydney. *C*, Synthesised by Mr. P. I. Mortimer, Division of Plant Industry, Canberra. *D*, Supplied by Professor Wain, Wye College, England.

§ Spectral shift too small to be measured.

[a] Behaghel, *J. prakt. Chem.*, 1926, **114**, 287. [b] Hayes and Branch, *J. Amer. Chem. Soc.*, 1943, **65**, 1555. [c] Matell and Lindenfors, *Acta Chem. Scand.*, 1957, **11**, 324. [d] Audus, *New Phytologist*, 1949, **48**, 97. [e] Van Overbeek, Blondeau, and Horne, *Plant Physiol.*, 1951, **26**, 687. [f] Wedding, Erickson, and Brannaman, *Plant Physiol.*, 1954, **29**, 64. [g] Burstrom, Sjoberg, and Hansen, *Acta Agr. Scand.*, 1956, **6**, 155. [h] Ketelaar, Gersmann, and Beck, *Rec. Trav. chim.*, 1952, **71**, 497.

The phenoxyacetic acids were supplied commercially except where otherwise stated (see Table 2). The phosphorus analogues [6] were supplied by Drs. M. H. Maguire and G. Shaw of the University of Technology, Sydney.

[6] Maguire and Shaw, *J.*, 1953, 1479; 1955, 1756; 1957, 311.

Results

Table 2 records pK' values determined in water by potentiometric (Pot.) and spectral (Spectr.) titration and in 50% ethanol by potentiometric titration for phenoxyacetic acid and a number of mono-, di-, and tri-chlorinated derivatives as well as for some 2 : 4-dichloro-substituted homologues. Where comparison is possible the agreement between the potentiometric and the spectroscopic technique is satisfactory.

Table 3 summarises pK values determined for a number of chloro-substituted phenoxymethylphosphonic acids, phenoxymethylphosphinic acids, and ethyl hydrogen (phenoxymethyl)phosphonates as well as for some phenoxyethyl and phenyl dihydrogen phosphates. In general the strongly acidic dissociation constants were determined spectroscopically. For the phenyl dihydrogen phosphates the potentiometric pK'_2 values reported in the literature

TABLE 3.

Parent	Subst.	λ_{mean} (Å)	pK_1 (Spectr.), 20° pK'_1 *	p$K°_1$ †	pK_2, 20° pK'_2 (Pot.) I ‡ ~0·02	pK'_2 (Spectr.) I ‡ ~0·01 ⟶ 0·02	Lit. values § pK'_1	Lit. values § pK'_2
Phenoxymethyl-phosphonic acid	—	2290	1·22	1·37	6·84	6·82	—	—
	2-Cl-	2320	1·30	1·43	6·83	6·80	—	—
	4-Cl-	—	*a*	—	6·82 [c]	*a*	—	—
	2 : 4-Cl_2-	2420	1·15	1·30	6·72	6·75	—	—
	2 : 6-Cl_2-	—	*b*	—	7·11	*b*	—	—
	2 : 4 : 5-Cl_3-	2450	1·10	1·26	6·59	6·56	—	—
	2 : 4 : 6-Cl_3-	—	*b*	—	7·07	*b*	—	—
Ethyl hydrogen (phenoxymethyl)-phosphonate	—	—	*a*	—	—	—	—	—
	2-Cl-	2310	0·71	0·96	—	—	—	—
	4-Cl-	2380	0·66	0·93	—	—	—	—
	2 : 4-Cl_2-	2400	0·65	0·92	—	—	—	—
	2 : 6-Cl_2-	—	*b*	—	—	—	—	—
	2 : 4 : 5-Cl_3-	2450	0·55	0·86	—	—	—	—
	2 : 4 : 6-Cl_3-	—	*b*	—	—	—	—	—
Phenoxymethyl-phosphinic acid	—	—	*a*	—	—	—	—	—
	4-Cl-	2380	0·77	1·00	—	—	—	—
	2 : 4-Cl_2-	2400	0·73	0·98	—	—	—	—
	2 : 4 : 5-Cl_3-	2450	0·67	0·94	—	—	—	—
Phenoxyethyl dihydrogen phosphate	—	—	*a*	—	*a*	*a*	—	—
	2-Cl-	—	*b*	—	6·58	*b*	2·03	6·55
	4-Cl-	—	*b*	—	6·58	*b*	2·03	6·50
Phenyl dihydrogen phosphate	—	—	*a*	—	*a*	*a*	—	—
	4-Cl-	2320	0·37	0·70	5·89	5·83	2·02	5·80
	2 : 4-Cl_2-	2350	0·28	0·65	5·76	5·68	2·03	5·63
	2 : 4 : 5-Cl_3-	2940	−0·1	0·53	5·47	5·48	2·03	5·30

[a] Compound not available. [b] Spectral shift too small to permit measurement. All this compound was used up in the potentiometric titration.

[c] pK' is equal to the pH at half-neutralisation. † Determined at various degrees of ionisation by use of H_- values.

‡ Approximate ionic strength at the point of half neutralisation.

§ Maguire and Shaw, *J.*, 1953, 1479.

agree well with those determined here spectroscopically, whilst the potentiometric pK'_1 values show very poor agreement with the spectroscopic values. The literature values were determined by potentiometric titration of a 0·02M-solution and were termed "approximate." No details as to the method of calculation were given.

In the case of the phenoxyethyl dihydrogen phosphates the spectral change associated with ionisation was too small for the spectroscopic method to be applied so that pK_1 values could not be determined. It was however readily applicable to the phenyl dihydrogen phosphates.

Discussion

The relative acid-strengthening effect of the phenoxy-group is shown in Table 4, which summarises pK'_1 values for various substituted acetic acids and methylphosphonic acids. This enhancement of acid strength arises primarily from the negative inductive effect of the phenoxy-group, which is of the same order as that of the iodo-group and considerably greater than that of the phenyl or hydroxyl groups.

XUM

The insertion of methylene groups between the phenoxy- and the ionising group markedly affects the acidic strength as would be expected from a consideration of the inductive field effect. Thus β-(2 : 4-dichlorophenoxy)propionic acid is *ca.* 1·5 pK units weaker than the corresponding acetic or α-substituted propionic acid and the insertion

TABLE 4.

R		CH_3	H	C_6H_5	HO	C_6H_5O †	I	Br	Cl
$R{\cdot}CH_2{\cdot}CO_2H$	pK'_1 ...	4·87 [a]	4·74 [a]	4·25 [a]	3·31 [b]	3·12	3·13 [a]	2·86 [a]	2·81 [a]
$R{\cdot}CH_2{\cdot}P(:O)(OH)_2$ *	pK'_1 ...	2·43 [c]	2·38 [c]	1·85 [c]	1·91 [d]	1·22	1·30 [d]	1·14 [d]	1·40 [d]
,,	pK'_2 ...	8·05 [c]	7·74 [c]	7·4 [c]	7·15 [d]	6·84	6·72 [d]	6·52 [d]	6·30 [d]

* See Freedman and Doak, *Chem. Rev.*, 1957, **57**, 479, for other pK values for substituted phosphonic acids. † Determined here.

[a] Watson, "Modern Theories of Organic Chemistry," Oxford Univ. Press, 1941, Table I, p. 27. [b] International Critical Tables, Vol. VI, p. 262. [c] Ref. 13. [d] Crofts and Kosolapoff, *J. Amer. Chem. Soc.*, 1953, **75**, 5738. [e] Lesfauries and Rumpf, *Bull. Soc. chim.*, 1950, 542.

of another methylene group weakens it by a further 0·4 pK unit to a value corresponding to that for butyric acid. Similarly chloro-substituted phenoxyethyl dihydrogen phosphates are weaker than the corresponding phenyl dihydrogen phosphates and are equivalent in strength to ethyl dihydrogen phosphate ($pK'_1 = 1{\cdot}60$, $pK'_2 = 6{\cdot}62$).[7] It appears therefore that the inductive effect of the phenoxy-group is almost eliminated by the insertion of two methylene groups and completely so by the insertion of three or more.

Chloro-substitution in the phenyl ring generally enhances the acidic strength, the magnitude depending on the number of chloro-groups and the distance of separation between the aromatic nucleus and the ionising group. In the phenoxyacetic acids and their phosphorus analogues the effect is so small as to be partially swamped by solvent effects [cf. the different order of strength of substituted phenoxyacetic acids in water and in 50% ethanol (Table 2)].

2 : 6-Disubstituted derivatives are exceptional in being weaker acids than their isomers and in some cases than their unsubstituted parent acid, *e.g.*, 2 : 6-dichloro- and 2 : 4 : 6-trichloro-phenoxyacetic acids and phenoxymethylphosphonic acids. This anomaly is reflected in a smaller intensity of the ultraviolet absorption bands than with other isomers.[3] It has been attributed [8] to steric hindrance's preventing the oxygen–methylene carbon bond's lying in the plane of the benzene ring with a consequent reduction in conjugation between the side-chain and the aromatic nucleus. This weakens the inductive pull of the phenoxy-group on the electrons associated with the acidic group and leads to an acid-weakening effect.

It is noteworthy that 2 : 6-disubstituted phenoxyacetic acids are generally inactive as auxins and have been claimed [9] to act as anti-auxins. Although such behaviour has been attributed to the chemical blocking of both *ortho*-positions, the fact that the substitution of the smaller fluoro-group for one of the *ortho*-chloro-groups in 2 : 4 : 6-trichlorophenoxyacetic acid restores auxin activity [10] suggests that the anomalous biological as well as physicochemical behaviour can be attributed to stereochemical factors.

The ethyl hydrogen phosphonates are *ca.* 0·4 pK unit stronger than the free acids, a similar effect having been observed [7] with phosphoric acid and its simple alkyl esters. This could not be attributed to an inductive or statistical effect, both of which would be acid-weakening, but rather, as in the case of the phosphate esters, to a solvation effect's stabilising the free acid relative to its ion more than the ester relative to its ion.

Substituted phosphinic acids are stronger than the corresponding phosphonic acids by *ca.* 0·3 pK unit. No accurate comparison of the relative strength of phosphinic and phosphonic acids has been reported previously, although Lesfauries and Rumpf's results [11]

[7] Kumler and Eiler, *J. Amer. Chem. Soc.*, 1943, **65**, 2355.
[8] Wiles, *Chem. Rev.*, 1956, **56**, 329; Burawoy and Chamberlain, *J.*, 1952, 2310.
[9] McRae and Bonner, *Plant Physiol.*, 1952, **27**, 834.
[10] Wain, *Science Progress*, 1956, **176**, 604.
[11] Lesfauries and Rumpf, *Compt. rend.*, 1949, **228**, 1018.

on the strength of substituted phenylphosphinic and phenylphosphonic acids are consistent with ours. This trend is again contrary to what would be expected from inductive and statistical considerations so that a solvation effect may be responsible, although in this case the possibility of differing resonance stabilisation energies cannot be ignored.

Unfortunately direct comparison is not possible between the phosphonic and phosphinic acids studied and the corresponding phosphates because of difficulties in preparing phenoxymethyl dihydrogen phosphates. The pK' values for *p*-chlorophenyl dihydrogen phosphate (0·37 and 5·83) can however be compared with that for *p*-chlorophenylphosphonic acid [12] (pK'_1 = 1·66 and pK'_2 = 6·75) from which it is clear that the phosphate is the stronger acid. A similar conclusion can be drawn from comparison in the alkyl series, *e.g.*, ethyl dihydrogen phosphate, pK'_1 = 1·60; pK'_2 = 6·62,[7] and ethylphosphonic acid, pK'_1 = 2·43; pK'_2 = 8·05.[13]

The spectral change accompanying the ionisation of the strong phosphorus-containing acids has a particular application to the measurement of the H_- acidity function in strongly acidic media. Some preliminary data for aqueous hydrochloric acid solutions pertinent to this investigation are shown in Table 1, and more detailed results will be discussed elsewhere.[3]

The pK values reported indicate that of the phosphorus-containing acidic groups the order of strength is phosphate > ethyl phosphonate > phosphinic acid > phosphonic acid.

The author thanks Miss I. Verners for experimental assistance.

Commonwealth Scientific and Industrial Research Organisation,
Division of Plant Industry, Canberra, Australia. [*Received, April 9th*, 1958.]

[12] Jaffe, Freedman, and Doak, *J. Amer. Chem. Soc.*, 1953, **75**, 2209.
[13] Crofts and Kosolapoff, *J. Amer. Chem. Soc.*, 1953, **75**, 3379.

---

868. *Synthetical Studies relating to Colchicine. Part I. Some Derivatives of* 1 : 2-*Benzo*cyclo*hept*-1-*en*-4-*one*.

By T. A. Crabb and K. Schofield.

1 : 2-Benzo*cyclo*hepta-1 : 3-diene was converted into the epoxide and thence into 1 : 2-benzo*cyclo*hept-1-en-4-one. 3-Methyl-1 : 2-benzo*cyclo*hept-1-en-4-one was prepared similarly, but ethyl β-(1 : 2-benzo*cyclo*hepta-1 : 3-dien-3-yl)propionate and methyl γ-(1 : 2-benzo*cyclo*hepta-1 : 3-dien-3-yl)-butyrate gave hydroxy-lactones rather than epoxides or ketones when treated with perbenzoic acid. The mixture of ethyl 1 : 2-benzo*cyclo*hepta-1 : 3-dien-3-ylacetate and its exocyclic isomer was epoxidised, and gave, after hydrolysis, some 4-oxo-1 : 2-benzo*cyclo*hept-1-en-3-ylacetic acid.

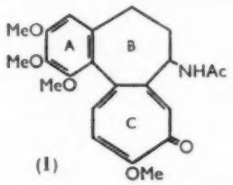
The last acid, its ethyl ester, ethyl β-(4-oxo-1 : 2-benzo*cyclo*hept-1-en-3-yl)-propionate, and its nitrile were obtained from the pyrrolidine-enamine derived from 1 : 2-benzo*cyclo*hept-1-en-4-one.

A large amount of work has been reported having as its aim either the synthesis of colchicine (I), or of compounds containing the colchicine skeleton. The most important studies in this field belong either to the "AC ⟶ ABC" or to the "AB ⟶ ABC" type, according to whether the starting materials contain rings A and C, or rings A and B substantially complete. This paper describes model experiments along the "AB ⟶ ABC" route, and corrects in two important respects a preliminary report.[1]

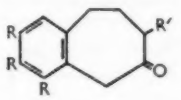
Previous workers using these lines have described the preparation of 1 : 2-benzo*cyclo*hept-1-en-4-one [2] (II; R = R′ = H), its trimethoxy-analogue [3] (II; R = OMe, R′ = H),

[1] Crabb and Schofield, *Chem. and Ind.*, 1958, 102.
[2] Page and Tarbell, *J. Amer. Chem. Soc.*, 1953, **75**, 2053.
[3] Rapoport and Campion, *ibid.*, 1951, **73**, 2239; Eschenmoser and Rennhard, *Helv. Chim. Acta*, 1953, **36**, 290; Walker, *J. Amer. Chem. Soc.*, 1955, **77**, 6699.

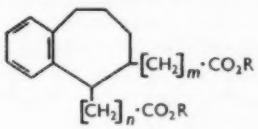
and the related acetamido-derivative [4] (II; R = OMe, R′ = NHAc). Several workers appear to share the aim of preparing compounds of type (III), for construction of ring c by cyclisation. Anderson and Greef [5] obtained an ester (III; R = Me, $m = 2$, $n = 1$) by well-known steps from 1 : 2-benzo*cyclo*hept-1-en-3-one, and Horton, Johnson, and Zollinger [6] prepared the analogue (III; R = Me, $m = n = 1$) by similar methods. Our own aim was initially similar to that of Anderson and Greef, having as its first target the discovery of a route to compounds of the type (VI; R = $[CH_2]_2{\cdot}CO_2Et$).



(I)



(II)



(III)

The original preparation [2] of the ketone (II; R = R′ = H) was inconvenient, and it seemed likely that this ketone might be more easily prepared from 1 : 2-benzo*cyclo*hep a 1 : 3-diene (IV; R = H), itself obtainable from the readily available 1 : 2-benzo*cyclo*hept-1-en-3-one by reduction to the alcohol and dehydration.[7] Treatment of the hydrocarbon (IV; R = H) with perbenzoic acid in chloroform provided the epoxide (V; R = H) in high yield. We stated earlier [1] that this epoxide was converted by magnesium bromide in ether into a mixture of ketones, (VI; R = H) and 1 : 2-benzo*cyclo*hept-1-en-3-one. This conclusion was based on bad experimentation. In fact, magnesium bromide converted the epoxide into the 4-ketone (VI; R = H) in high yield. This undirectional rearrangement of the epoxide was to be expected by analogy with the reactions of the oxides from indene, 1 : 2-dihydronaphthalene and related compounds, and the 3 : 4-epoxide [8] from 1 : 2-benzo*cyclo*octa-1 : 3-diene. In contrast, the use of the boron trifluoride–ether complex to isomerise the epoxide, whilst giving mainly 1 : 2-benzo*cyclo*-hept-1-en-4-one, did produce a small amount of the isomeric 3-ketone, as was proved by isolation of the very characteristic red 2 : 4-dinitrophenylhydrazone of the latter. In addition, two other unidentified crystalline products were formed. This complex reaction was not examined further.

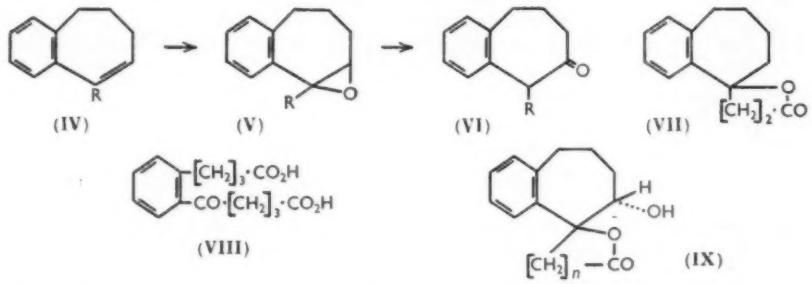
The epoxide could also be converted into the ketone (VI; R = H) through the intermediate crystalline 1 : 2-benzo*cyclo*hept-1-en-4-ol, formed by reduction with lithium aluminium hydride. The alcohol was oxidised with chromic acid in pyridine or acetic acid, though we did not find good conditions for avoiding over-oxidation on the one hand, or contamination of the product with unchanged alcohol on the other. Oppenauer oxidation of the alcohol was very satisfactory.

These experiments encouraged us to attempt the direct synthesis of compounds of the type (VI) in which R was an alkyl or ethoxycarbonylalkyl group, by using the same sequence of reactions with compounds (IV) already carrying the desired side-chain. For the simplest case, 3-methyl-1 : 2-benzo*cyclo*hepta-1 : 3-diene (IV; R = Me) was already known.[7] On ozonolysis it gave no detectable amount of 1 : 2-benzo*cyclo*hept-1-en-3-one; if the exocyclic analogue of (IV; R = Me) was present it must have been in small amount. Epoxidation of the diene gave the 4-ketone (VI; R = Me) directly and in good yield, the intermediate epoxide not being encountered. Evidence for the ketonic nature of the product came from the ready formation of a semicarbazone [the oxide (V; R = H)

[4] Buchanan and Sutherland, *J.*, 1957, 2334.
[5] Anderson and Greef, *J. Amer. Chem. Soc.*, 1952, **74**, 5203.
[6] Horton, Johnson, and Zollinger, *ibid.*, 1954, **76**, 4587.
[7] Horn and Rapson, *J.*, 1949, 2421; Treibs and Klinkhammer, *Chem. Ber.*, 1950, **83**, 367.
[8] Tchoubar, *Compt. rend.*, 1942, **214**, 117; Kornfeld, Fornefeld, Kline, Mann, Morrison, Jones, and Woodward, *J. Amer. Chem. Soc.*, 1956, **78**, 3087; Huisgen, Rauenbusch, and Seidl, *Chem. Ber.*, 1957, **90**, 1958.

XUM

gave no derivatives with carbonyl reagents], and from the characteristic infrared band at 1707 cm.$^{-1}$ (for seven-membered ring ketones 1725—1705 cm.$^{-1}$ is reported [9]). With 2 : 4-dinitrophenylhydrazine the ketone, as obtained from epoxidation, gave a yellow derivative contaminated with traces of a red solid. The latter was difficult to eliminate (it was not 2 : 4-dinitrophenylhydrazine for it escaped from passage over a column of bentonite–kieselguhr), and to obtain the quite pure 2 : 4-dinitrophenylhydrazone it proved necessary to use a ketone obtained from hydrolysis of the semicarbazone. The direct isolation of ketones from epoxidations has been reported before.[10]



Next we turned to ethyl 1 : 2-benzo*cyclo*hepta-1 : 3-dienylacetate (IV; R = $\cdot CH_2 \cdot CO_2Et$). This structure was assigned by Anderson and Wang [11] to the unsaturated ester obtained by dehydrating with formic acid the Reformatsky product from ethyl bromoacetate and 1 : 2-benzo*cyclo*hept-1-en-3-one. The position of the double-bond was assigned on the basis of the ultraviolet absorption maximum at 243 mμ. Accepting this assignment, we at first mistook the material formed by epoxidising the unsaturated ester for a homogeneous compound. Later, accumulated evidence showed that it could not be homogeneous, and, in fact, ozonisation of the unsaturated material from the Reformatsky–hydrogenation–dehydration sequence produced some 1 : 2-benzo*cyclo*hept-1-en-3-one. This, with what follows, proves the unsaturated material to be a mixture of the ester (IV; R = $\cdot CH_2 \cdot CO_2Et$) and its exocyclic isomer. The product of epoxidation of this mixture was an oil which could not be fractionated by distillation. The infrared absorption spectrum of the oil indicated the presence of a ketone, and furthermore a yellow 2 : 4-dinitrophenylhydrazone, m. p. 106—107°, identical with that of authentic ethyl 4-oxo-1 : 2-benzo*cyclo*hept-1-en-3-ylacetate (VI; R = $\cdot CH_2 \cdot CO_2Et$) (see below) could be obtained from the mixture. Alkaline hydrolysis of the epoxidation mixture gave 25% of 4-oxo-1 : 2-benzo*cyclo*hept-1-en-3-ylacetic acid, together with another acid. Whilst the epoxidation product from the mixed esters was thus proved to contain some ethyl 4-oxo-1 : 2-benzo*cyclo*hept-1-en-3-ylacetate, the other constituent, or constituents, of the epoxidation mixture have not been identified. We are examining this problem further.

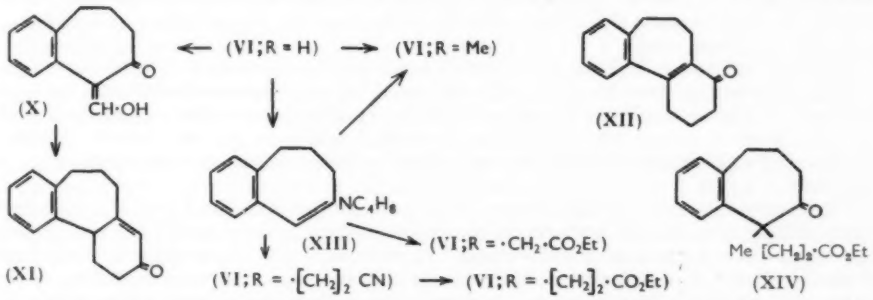
Ethyl β-(1 : 2-benzo*cyclo*hepta-1 : 3-dien-3-yl)propionate and the analogous butyrate (IV; R = $\cdot[CH_2]_2 \cdot CO_2Et$ and $\cdot[CH_2]_3 \cdot CO_2Et$ respectively), when submitted to similar treatment, gave interesting but not very useful results. The first of these esters was prepared by acid hydrolysis of the crude half-ester from the Stobbe condensation [12] of diethyl succinate with 1 : 2-benzo*cyclo*hept-1-en-3-one, followed by esterification. [The *spiro*-lactone (VII) was also formed in the hydrolysis.] Ozonolysis of the unsaturated ester showed the double bond to be endocyclic. The ester (IV; R = $\cdot[CH_2]_3 \cdot CO_2Et$) resulted from hydrogenation and dehydration of the Reformatsky product from methyl γ-bromocrotonate and 1 : 2-benzo*cyclo*hept-1-en-3-one, the methods used being similar

[9] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen and Co. Ltd., London 1954.
[10] English and Cavaglieri, *J. Amer. Chem. Soc.*, 1943, **65**, 1085; Mills and Schofield, *J.*, 1956, 4213.
[11] Anderson and Wang, *J. Org. Chem.*, 1954, **19**, 277.
[12] Cook, Philip, and Somerville, *J.*, 1948, 164.

to those described by Anderson and Greef.[13] Hydrogenation of the crude Reformatsky product was essential, for distillation of the intermediate hydroxy-ester caused dehydration. Again, ozonolysis of the unsaturated ester (IV; R = $\cdot[CH_2]_3\cdot CO_2Et$) proved the essential absence of the exocyclic isomer; no 1 : 2-benzo*cyclo*hept-1-en-3-one could be detected, but a crystalline acid, probably (VIII), resulted.

Epoxidation of the esters (IV; R = $\cdot[CH_2]\cdot CO_2Et$ and $\cdot[CH_2]_3\cdot CO_2Et$) in the usual way gave homogeneous products, in the first case a solid and in the second an oil, in good yield. These products showed no ketonic properties, nor could they be converted into ketones by acid treatment. The infrared absorption spectrum of the solid showed bands at 1755 and 3510 cm.$^{-1}$, appropriate to a γ-lactone and a hydroxyl group respectively.[9] The corresponding bands for the oil were at 1735 and 3480 cm.$^{-1}$. On this evidence the structures (IX; $n = 2$ and 3) are provisionally assigned to these compounds. A related case of lactone formation during oxidation of β-3-indenylpropionic acid was reported recently.[14]

These attempts to prepare derivatives of 1 : 2-benzo*cyclo*hept-1-en-4-one with ethoxycarbonylalkyl residues at the 3-position did not promise well. We therefore examined some reactions of the ketone (VI; R = H) itself. Methylation with methyl iodide–sodium methoxide, the most satisfactory of several reagents examined, gave a ketone (VI; R = Me) in moderate yield, characterised as its semicarbazone which was identical with that from the ketone obtained by epoxidising the hydrocarbon (IV; R = Me). Attempted reaction of the parent ketone (VI; R = H) with ethyl β-bromopropionate under a variety of conditions, or with diethyl carbonate in the presence of sodium hydride, failed. In contrast, the ketone reacted readily with ethyl formate and sodium ethoxide to give a product which, from the proved direction of the methylation just described as well as on general grounds, we take to be 3-hydroxymethylene-1 : 2-benzo*cyclo*hept-1-en-4-one (X). With methyl vinyl ketone this compound (X) reacted to give, after hydrolysis of the crude product, the tricyclic ketone (XI) (isolated as the 2 : 4-dinitrophenylhydrazone) isomeric with that (XII) formed by cyclising γ-(1 : 2-benzo*cyclo*hept-1 : 3-dien-3-yl)-butyric acid with zinc chloride in acetic anhydride–acetic acid. Most usefully, 1 : 2-benzo*cyclo*hept-1-en-4-one (VI; R = H) readily formed the enamine (XIII) with pyrrolidine. On treatment with methyl iodide in dioxan, followed by the usual hydrolysis,[15] the enamine was converted into 3-methyl-1 : 2-benzo*cyclo*hept-1-en-4-one. In the same way,



use of ethyl bromoacetate gave the crystalline ester (VI; R = $\cdot CH_2\cdot CO_2Et$), hydrolysis of which produced the keto-acid, identical with one of the products of hydrolysis of the mixture of esters derived from the epoxidation already described. Our original aim was finally achieved by treating the enamine with acrylonitrile, the keto-nitrile (VI; R = $\cdot[CH_2]_2\cdot CN$) being formed in good yield. Acid-alcoholysis converted this into the

[13] Anderson and Greef, *J. Amer. Chem. Soc.*, 1952, **74**, 5124.
[14] Howell and Taylor, *J.*, 1957, 3011.
[15] Robinson, *J.*, 1916, 1038; Stork, *J. Amer. Chem. Soc.*, 1954, **76**, 2029.

XUM

desired keto-ester (VI; R = $\cdot[CH_2]_2\cdot CO_2Et$). The possibility of using this ester and the hydroxymethylene compound (X) in a closer approach to the colchicine skeleton, and the extension of these reactions to the trimethoxylated series, are being studied.

3-Methyl-1 : 2-benzo*cyclo*hept-1-en-4-one being readily available, we examined a few of its reactions. Although the reaction product was not purified, it was clear from the alkali-insolubility of the major portion of it that nitrosation of the ketone proceeded mainly at the 3-position, as was expected. In contrast to 1 : 2-benzo*cyclo*hept-1-en-4-one itself, the methylated ketone reacted with ethyl β-bromopropionate, giving (presumably) the keto-ester (XIV). With acrylonitrile in presence of benzyltrimethylammonium hydroxide the methylated ketone gave a mixture of mono- and di-substituted derivatives, as shown by their hydrolysis to a liquid mono- and a crystalline di-carboxylic acid.

Experimental

3 : 4-*Epoxy*-1 : 2-*benzo*cyclo*hept*-1-*ene*.—A cooled solution of the 1 : 3-diene [7] (35 g.) in chloroform (100 ml.) was stirred and treated with perbenzoic acid (40·6 g.) in chloroform (640 ml.) at such a rate that the temperature did not rise above 5°. The solution was then stirred at 0° for 8 hr., kept overnight at 5° (titration showed that 78% of the perbenzoic acid was consumed in 8 hr.), and then washed with sodium hydroxide solution and with water. Distillation of the dried (Na_2SO_4) solution gave the *epoxide* (32 g.), b. p. 80°/0·04 mm., n_D^{17} 1·5550 (Found: C, 82·2; H, 7·9. $C_{11}H_{12}O$ requires C, 82·5; H, 7·6%).

1 : 2-*Benzo*cyclo*hept*-1-*en*-4-*ol*.—The epoxide (16 g.) in dry ether (32 ml.) was added during 15 min. to a vigorously stirred suspension of lithium aluminium hydride (8 g.) in the same solvent (160 ml.), gentle refluxing being thus maintained. The mixture was heated under reflux for 1 hr., then decomposed with water. Isolation of the product in the usual way, and crystallisation from light petroleum (b. p. 40—60°) gave the *alcohol* (14 g.) as needles, m. p. 71° (Found: C, 81·2; H, 8·6. $C_{11}H_{14}O$ requires C, 81·4; H, 8·7%). The p-*nitrobenzoate* formed needles, m. p. 92—93° (Found: C 69·2; H, 5·7. $C_{18}H_{17}O_4N$ requires C, 69·4; H, 5·5%), from light petroleum (b. p. 40—60°).

1 : 2-*Benzo*cyclo*hept*-1-*en*-4-*one*.—(i) Rearrangement of the epoxide (8·4 g.) with magnesium bromide under the conditions used by Kornfeld *et al.*[8] gave the ketone (7·6 g.), b. p. 82°/0·2 mm., n_D^{20} 1·5552 [2 : 4-dinitrophenylhydrazone, m. p. 169·5° (reported [2] m. p. 169—170°) (Found: C, 59·6; H 4·9. Calc. for $C_{17}H_{16}O_4N_4$: C, 60·0; H, 4·7%)]. In a separate experiment the crude rearrangement product was treated with saturated sodium hydrogen sulphite solution. Decomposition of the resulting compound in the usual way and conversion of the total ketone into the 2 : 4-dinitrophenylhydrazone revealed no trace of the red derivative of 1 : 2-benzo-*cyclo*hept-1-en-3-one.

(ii) Boron trifluoride–ether complex (7·2 g.) was added in one portion to a solution of the epoxide (6 g.) in dry ether (60 ml.). After the initial vigorous reaction the mixture was kept overnight and then washed with sodium hydroxide solution and water. Concentration of the dried solution gave a solid (0·35 g.) which formed needles, m. p. 190° (Found: C 82·8; H, 7·8. $C_{11}H_{12}O$ requires C, 82·5; H, 7·6%), from ethanol. It gave a semicarbazone m. p. 208—209°.

The residue left after removal of the solid, m. p. 190°, was distilled, giving a colourless liquid (2·3 g.), b. p. 80—90°/0·05 mm., and a product (3·2 g.), b. p. >160°/0·05 mm., which gave small white crystals, m. p. 145° (Found: C, 82·2; H, 7·6%), from ethanol. Treatment of the liquid with 2 : 4-dinitrophenylhydrazine in the usual way, and recrystallisation of the orange product from methanol, gave a mixture of fine yellow needles of 1 : 2-benzo*cyclo*hept-1-en-4-one 2 : 4-dinitrophenylhydrazone (m. p. and mixed m. p. 169—170°) and shorter red crystals of 1 : 2-benzo*cyclo*hept-1-en-3-one 2 : 4-dinitrophenylhydrazone (m. p. and mixed m. p. 205—206°), which were separated mechanically.

(iii) 1 : 2-Benzo*cyclo*hept-1-en-4-ol (3·35 g.), aluminium *iso*propoxide (10 g.), *cyclo*hexanone (83·8 ml.), and toluene (250 ml.) were heated together under reflux for 2 hr. The usual processing afforded a liquid (10 g.), b. p. 125—140°/15 mm., which was shaken with saturated sodium hydrogen sulphite solution for 2 hr. The precipitate was washed with ether and shaken with sodium carbonate solution. The ketone, isolated by ether-extraction, was a colourless liquid (3·1 g.), b. p. 128—132°/15 mm., which became pale yellow when kept.

XUM

An attempt to use acetone in benzene solution for the oxidation gave no ketone.

(iv) The alcohol (12 g.) in pyridine (120 ml.) was added to a slurry [16] of chromium trioxide (20·4 g.) in pyridine (204 ml.). The mixture was stirred overnight at room temperature, poured into water, and extracted with ether. Purification through the bisulphite compound gave the ketone (7 g.) and unchanged alcohol (4 g.).

Alternatively, the alcohol (18 g.) in acetic acid (20 ml.) was treated during 5 hr. with chromium trioxide (13·5 g.) in acetic acid (20 ml.) and water (10 ml.), the temperature being kept below 5°. After being stirred for 12 hr. at room temperature the solution was diluted with water and extracted with ether. Distillation gave the ketone (13·5 g.), b. p. 82°/0·2 mm.

3-Methyl-1 : 2-benzocyclohept-1-en-4-one.—(i) An ice-cooled mixture of 1 : 2-benzo*cyclo*hept-1-en-4-one (2 g.), dry methanol (2·2 ml.), and methyl iodide (1·1 ml.) was stirred under nitrogen during the addition (1 hr.) of a solution of sodium (0·28 g.) in methanol (4·4 ml.). The solution was stirred for 2 hr. more, boiled for 2 min., treated with dilute sulphuric acid, and extracted with ether. Distillation gave an oil (1·4 g.), b. p. 134°/15 mm. This (0·3 g.) gave the *semicarbazone* (0·2 g.) which from ethanol formed small needles, m. p. and mixed m. p. with the specimen described below, 208° (Found: C, 67·5; H, 7·5; N, 18·2. $C_{13}H_{17}ON_3$ requires C, 67·5; H, 7·4; N, 18·2%). The yield of the methylated ketone, estimated by semicarbazone formation, was 42%. Corresponding yields for methylations carried out with potassium–benzene and with sodium *iso*propoxide–propan-2-ol were 16% and 26%, respectively.

(ii) 3-Methyl-1 : 2-benzo*cyclo*hept-1-en-3-ol (prepared from 1 : 2-benzo*cyclo*hept-1-en-3-one in 74% yield by the method of Treibs and Klinkhammer [7]) gave on dehydration 68% of 3-methyl-1 : 2-benzo*cyclo*hepta-1 : 3-diene ($\lambda_{max.}$ 244 mμ, $\log_{10}\varepsilon$ 3·98). Treatment of this compound (1·5 g.) in ethyl acetate (20 ml.) with ozone, followed by hydrogenation of the solution in presence of platinum oxide (0·1 g.), gave an acid fraction (1·4 g.) and a neutral yellow oil (0·1 g.). From neither of these could a pure 2 : 4-dinitrophenylhydrazone be obtained.

3-Methyl-1 : 2-benzo*cyclo*hepta-1 : 3-diene (6 g.) in chloroform (25 ml.) was treated with perbenzoic acid (6·3 g.) in chloroform (150 ml.) at 0—5°, and the solution was then stirred at this temperature for 10 hr. and kept overnight. Working up gave *3-methyl-1 : 2-benzocyclohept-1-en-4-one* (5·1 g.), b. p. 120°/1·5 mm., $n_D^{15\cdot5}$ 1·5621 (Found: C, 82·6; H, 8·0. $C_{12}H_{14}O$ requires C, 82·7; H, 8·1%). The semicarbazone, m. p. 208°, was identical with that described above. The pure semicarbazone (0·22 g.) was heated at 95° for 10 min. with 6N-hydrochloric acid (50 ml.). The ketone, recovered by ether-extraction, gave in the usual way the yellow *2 : 4-dinitrophenylhydrazone* which formed platelets, m. p. 150—151° (Found: C, 60·7; H, 5·0. $C_{18}H_{16}O_4N_4$ requires C, 61·0; H, 5·1%), from methanol.

Experiments with the Mixture of Ethyl 1 : 2-Benzocyclohepta-1 : 3-dien-3-ylacetate and 1 : 2-Benzocyclohept-3-ylidenacetate.—The mixture was obtained in 62% yield by Anderson and Wang's method.[11]

Ozonisation of the mixture (1·4 g.) in the usual way gave a viscous, oily acid (1·4 g.) (of which the tarry 2 : 4-dinitrophenylhydrazone could not be purified) and a yellow neutral oil (0·5 g.). The latter provided 0·45 g. of pure 1 : 2-benzo*cyclo*hept-1-en-3-one 2 : 4-dinitrophenylhydrazone as fine red-bronze needles, m. p. and mixed m. p. 206° (from methanol–chloroform) (Found: C, 59·7; H, 4·7. Calc. for $C_{17}H_{16}O_4N_4$: C, 60·0; H, 4·7%).

The mixed esters (33 g.) in chloroform (50 ml.) were oxidised in the usual way with perbenzoic acid (24 g.) in chloroform (560 ml.). The product was a colourless liquid (25 g.), b. p. 136°/0·8 mm., n_D^{20} 1·5298 (Found: C, 73·5; H, 7·3. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%), $\nu_{max.}$ 1735 and 1710 cm.$^{-1}$. With 2 : 4-dinitrophenylhydrazine this liquid (1 g.) gave a mixture of yellow and red crystals (0·32 g.). These could not be separated by crystallisation, but on passing a solution of the mixture (0·2 g.) in chloroform over a column of bentonite–kieselguhr the yellow 2 : 4-dinitrophenylhydrazone (0·17 g.) was obtained. From ethanol it formed silky yellow needles, m. p. 106—107°, identical with ethyl 4-oxo-1 : 2-benzo*cyclo*hept-1-en-3-ylacetate 2 : 4-dinitrophenylhydrazone (see below).

The epoxidation product (11 g.) was boiled for 10 hr. with potassium hydroxide (30 g.) in aqueous ethanol (200 ml.). The mixture was acidified and the product was isolated with ether. Concentration of the extract gave *4-oxo-1 : 2-benzocyclohept-1-en-3-ylacetic acid* (2·5 g.), m. p. 132—133° after crystallisation from tetrahydrofuran–light petroleum (b. p. 40—60°) (Found: C, 70·8; H, 6·7. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·5%); distillation of the residue from the

[16] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.

extract gave a very viscous *acid* (5·4 g.), b. p. 128°/0·06 mm., n_D^{14} 1·5776 (Found: C, 76·7; H, 7·2. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4%).

Ethyl β-(1 : 2-*Benzo*cyclo*hepta*-1 : 3-*dien*-3-*yl*)*propionate*.—The crude half ester (13 g.) resulting from the reaction between diethyl succinate and 1 : 2-benzo*cyclo*hept-1-en-3-one,[12] was boiled with acetic acid (91 ml.), concentrated hydrochloric acid (45·5 ml.), and water (65 ml.) under nitrogen for 4 hr. The mixture was concentrated under reduced pressure and extracted with ether. The ether solution was extracted with sodium hydrogen carbonate solution. Acidification of the alkaline solution, followed by ether-extraction, gave the crude acid as a viscous brown oil (7 g.). Concentration of the neutral ether extract gave the spiro-*lactone* (VII) (3 g.) which formed needles, m. p. 134° (Found: C, 77·2; H, 7·2. $C_{14}H_{16}O_2$ requires C, 77·7; H, 7·4%), from ether.

The crude acid (14 g.) was boiled for 12 hr. with absolute ethanol (40 ml.) and concentrated sulphuric acid (1 ml.). Working up gave the *ester* (11·5 g.), b. p. 120°/0·1 mm., $n_D^{18·5}$ 1·5327 (Found: C, 79·2; H, 8·4. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·3%) ($\lambda_{max.}$ 241 mμ, $\log_{10}$ ε 3·93). Ozonolysis of the ester (0·5 g.) in the usual way gave an acid fraction (0·5 g.), and a neutral oil (0·05 g.) from which a 2 : 4-dinitrophenylhydrazone could not be prepared.

The Lactone (IX; $n = 2$).—The above ester (3·9 g.) in chloroform (30 ml.) was treated with perbenzoic acid (2·7 g.) in chloroform (40 ml.) as described above. The *lactone* (3 g.) formed plates, m. p. 138—139° (Found: C, 72·5; H, 7·0. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%), from ethanol.

Methyl γ-(1 : 2-*Benzo*cyclo*hepta*-1 : 3-*dien*-3-*yl*)*crotonate*.—1 : 2-Benzo*cyclo*hept-1-en-3-one (20 g.), amalgamated zinc (25 g.), methyl γ-bromocrotonate (22·5 g.), dry ether (50 ml.), dry benzene (50 ml.), and a crystal of iodine were heated under reflux. Three additions of zinc (12·5 g.) and methyl bromocrotonate (7·5 g.) were made at hourly intervals, and after the last addition the mixture was boiled for 2 hr. more. It was then poured into iced dilute acetic acid, and the product was extracted with ether. The extract was washed with 1% ammonia solution, water, and saturated brine, and then dried (Na_2SO_4). Distillation gave the *ester* as a golden-yellow oil (12 g.), b. p. 122°/0·05 mm., $n_D^{17·3}$ 1·5820 (Found: C, 78·8; H, 7·4. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·5%).

Methyl γ-(1 : 2-*Benzo*cyclo*hept*-1-*en*-3-*yl*)*butyrate*.—The unsaturated ester (2 g.) was shaken with hydrogen in the presence of ethanol (8 ml.) and Raney nickel (1 g.). Filtration and distillation gave the *ester* (1·2 g.), b. p. 120°/2 mm., n_D^{17} 1·5309 (Found: C, 79·0; H, 8·6. $C_{16}H_{22}O_2$ requires C, 78·0; H, 9·0%).

Methyl γ-(3-*Hydroxy*-1 : 2-*benzo*cyclo*hept*-1-*en*-3-*yl*)*butyrate*.—The Reformatsky reaction was repeated as described above, but at the end of the reaction the solvent was removed under reduced pressure and the crude product was shaken with ethanol (500 ml.) and Raney nickel (15 g.) under hydrogen. Filtration and distillation gave the *hydroxy-ester* (12 g.), b. p. 136°/0·05 mm., n_D^{18} 1·5426 (Found: C, 73·6; H, 8·1. $C_{16}H_{22}O_3$ requires C, 73·3; H, 8·4%).

Methyl γ-(1 : 2-*Benzo*cyclo*hepta*-1 : 3-*dien*-3-*yl*)*butyrate*.—The hydroxy-ester (12 g.) and 98% formic acid (90 ml.) were heated on the water-bath for 30 min. The diluted solution was extracted with benzene, and the extract was washed with sodium carbonate solution and dried. Distillation gave the ester as a colourless liquid (8·6 g.), b. p. 110°/0·05 mm., n_D^{17} 1·5439 (Found: C, 79·2; H, 8·4. Calc. for $C_{16}H_{20}O_2$: C, 78·7; H, 8·3%), which became pale yellow when kept. From 1 : 2-benzo*cyclo*hept-1-en-3-one (20 g.), without purification of the hydroxy-ester, this method gave the unsaturated ester in 30·5% overall yield.

The unsaturated ester (0·9 g.) in ethyl acetate (20 ml.) was ozonised in the usual way. After hydrogenation the solution was filtered, diluted with ether, and extracted with N-sodium hydroxide. The ether retained a neutral yellow oil (0·44 g.) which contained no 1 : 2-benzo-*cyclo*hept-1-en-3-one. The alkaline extract was acidified and extracted with ether. Removal of the ether and recrystallisation of the residue from this solvent gave needles of an *acid*, m. p. 116—117° (Found: C, 64·2; H, 6·5. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5%).

The Lactone (IX; $n = 3$).—The preceding unsaturated ester (9·25 g.) in chloroform (50 ml.) was treated in the usual way at 0—5° with perbenzoic acid (6·5 g.) in chloroform (125 ml.). (Titration showed that after 8 hr. 84% of the perbenzoic acid had been consumed.) After 15 hr. more at 5° the solution was processed as before. Distillation gave the *lactone* (7·2 g.), b. p. 145°/0·01 mm. (Found: C, 74·0; H, 7·2. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%).

γ-(1 : 2-*Benzo*cyclo*hept*-1-*en*-3-*yl*)*butyric Acid*.—The ester (IV; R = ·$[CH_2]_3$·CO_2Me) (9 g.), sodium hydroxide (7 g.), and 50% aqueous ethanol (30 ml.) were boiled together for 10 hr.

XUM

Acidification and extraction with ether isolated the *acid* (7 g.), b. p. 154—156°/0·1 mm., n_D^{16} 1·5588 (Found: C, 78·3; H, 8·0. $C_{16}H_{18}O_2$ requires C, 78·2; H, 7·9%), which became yellow when kept.

1′ : 2′ : 3′ : 4′-*Tetrahydro*-1 : 2-3 : 4-*dibenzo*cyclo*hepta*-1 : 3-*dien*-1′-*one* (XII).—The acid (6 g.), acetic anhydride (96 ml.), acetic acid (5 ml.), and a solution (5 ml.) of zinc chloride in acetic acid (20 mg./ml.) were kept together under nitrogen for 20 hr. The solution was then boiled for 2½ hr., concentrated under reduced pressure, diluted with water and extracted with ether. The washed (sodium hydrogen carbonate, water) and dried (Na_2SO_4) extract was distilled, giving the *ketone* as a yellow oil (4 g.), b. p. 122°/0·07 mm., n_D^{18} 1·6038 (Found: C, 83·8; H, 7·8. $C_{15}H_{16}O$ requires C, 84·9; H, 7·6%).

The 2 : 4-*dinitrophenylhydrazone*, m. p. 242° (Found: C, 64·3; H, 5·4. $C_{21}H_{20}O_4N_4$ requires C, 64·3; H, 5·1%), formed small red crystals from benzene.

3-*Hydroxymethylene*-1 : 2-*benzo*cyclo*hept*-1-*en*-4-*one*.—Ethyl formate (4·4 g.) in dry benzene (47·5 ml.) was added under nitrogen to powdered sodium methoxide (from 1·43 g. of sodium) which had previously been baked at 200° for 2 hr. under reduced pressure. The mixture was cooled in ice and treated with 1 : 2-benzo*cyclo*hept-1-en-4-one (4·8 g.) in benzene (50 ml.). The whole was allowed to reach room temperature and then heated at 95° for 2 hr. Water was added and the benzene layer was extracted with N-sodium hydroxide. Acidification of the alkaline solution, extraction with ether, and distillation gave the *hydroxymethylene compound* (4 g.), b. p. 92°/0·05 mm., n_D^{20} 1·5960 (Found: C, 76·0; H, 6·5. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%).

2 : 1′ : 2′ : 3′-*Tetrahydro*-1 : 2-3 : 4-*dibenzo*cyclo*hepta*-1 : 3-*dien*-3′-*one* (XI).—The hydroxymethylene compound (2 g.), methyl vinyl ketone (1·4 g.), potassium hydroxide (40 mg.), and anhydrous methanol (10 ml.) were boiled together for 6 hr. After concentration the mixture was diluted with water and extracted with ether. The ether contained a brown oil (2 g.) which was boiled for 2 hr. with acetic acid (25 ml.), hydrochloric acid (15 ml.), and water (7·5 ml.) under nitrogen. The solution was diluted with water and extracted with ether, and the extract was washed with sodium hydrogen carbonate solution. Distillation gave a colourless oil, b. p. 140—150°/0·1 mm., which provided a 2 : 4-*dinitrophenylhydrazone* as scarlet crystals, m. p. 209—210° (Found: C, 64·1; H, 5·2. $C_{21}H_{20}O_4N_4$ requires C, 64·3; H, 5·1%), from ethanol.

Reactions of 4-*Pyrrolidino*-1 : 2-*benzo*cyclo*hepta*-1 : 3-*diene* (XIII).—(i) *With methyl iodide*. 1 : 2-Benzo*cyclo*hept-1-en-4-one (1 g.), pyrrolidine (0·5 g.), and benzene (20 ml.) were heated under reflux in an apparatus provided with a water-separator. The reaction was complete in 30 min.; boiling was carried on for 1 hr. in all. The oil left when benzene was removed was heated with dioxan (10 ml.) and methyl iodide (8 ml.) at 95° for 30 hr.; a dark oil separated during the reaction. The mixture was left overnight with water, then extracted with ether. Removal of the ether and conversion of the residue into the semicarbazone, m. p. and mixed m. p. 207—208°, showed that 3-methyl-1 : 2-benzo*cyclo*hept-1-en-4-one had been formed in about 40% yield.

(ii) *With ethyl bromoacetate*. The enamine (XIII) (from 4 g. of ketone), ethyl bromoacetate (6·4 g.), and dioxan (40 ml.) were boiled together for 2 days. Working up as before gave *ethyl* 4-*oxo*-1 : 2-*benzo*cyclo*hept*-1-*en*-3-*ylacetate* (2·4 g.), b. p. 146°/0·2 mm., n_D^{16} 1·5321, plates [from light petroleum (b. p. 40—60°)], m. p. 64° (Found: C, 73·9; H, 7·7. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as silky yellow needles, m. p. 106° (Found: C, 58·9; H, 5·9; N, 13·1. $C_{21}H_{22}O_6N_4$ requires C, 59·1; H, 5·2; N, 13·1%), identical with the compound already described. Boiled for 12 hr. with potassium hydroxide (3 g.) in 50% aqueous ethanol (20 ml.), the ester (1 g.) gave the acid (0·8 g.) as white crystals (m. p. and mixed m. p. with the compound described above, 132°) from ether–light petroleum (b. p. 40—60°).

(iii) *With acrylonitrile*. The enamine (from 3·5 g. of ketone), acrylonitrile (4 g.), and dioxan (20 ml.), boiled together for 2 days and worked up as before, gave 3-2′-*cyanoethyl*-1 : 2-*benzo*cyclo*hept*-1-*en*-4-*one* (2·8 g.) as white needles, m. p. 76—77° (Found: C, 78·8; H, 7·3; N, 6·5. $C_{14}H_{15}ON$ requires C, 78·8; H, 7·1; N, 6·6%), from ether–light petroleum (b. p. 40—60°).

The keto-nitrile (2·8 g.) and ethanol (50 ml.) which had been saturated at 0° with hydrogen chloride were boiled together for 12 hr. Filtration, dilution with water, extraction with ether, and distillation gave *ethyl* β-(4-*oxo*-1 : 2-*benzo*cyclo*hept*-1-*en*-3-*yl*)*propionate* (2 g.), b. p. 136—138°/0·08 mm., n_D^{17} 1·5278 (Found: C, 73·3; H, 7·3. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%). The 2 : 4-*dinitrophenylhydrazone* formed fine yellow needles, m. p. 101° (Found: C, 60·5; H, 5·5. $C_{22}H_{24}O_6N_4$ requires C, 60·0; H, 5·5%), from methanol.

XUM

Ethyl β-(3-*Methyl*-4-*oxo*-1 : 2-*benzo*cyclo*hept*-1-*en*-3-*yl*)*propionate*.—The methylated ketone (4·35 g.), powdered potassium (0·97 g.), and benzene (50 ml.) were stirred together overnight. Ethyl β-bromopropionate (5 g.) was added, and the mixture was set aside for 24 hr., and then boiled for 4 hr. The usual processes gave the *propionate* (0·7 g.), b. p. 122°/0·05 mm., n_D^{18} 1·5380 (Found: C, 75·4; H, 8·5. $C_{17}H_{22}O_3$ requires C, 74·4; H, 8·1%).

Reaction of 3-*Methyl*-1 : 2-*benzo*cyclo*hept*-1-*en*-4-*one with Acrylonitrile*.—The ketone (1 g.) in dioxan (7·5 ml.) was cooled and shaken during the addition first of 40% benzyltrimethylammonium hydroxide solution (1 c.c.) and then of acrylonitrile (0·5 g.). The mixture was shaken at room temperature for 48 hr., acidified, and concentrated under reduced pressure. The residual oil, isolated with ether, was boiled with 20% potassium hydroxide solution (30 ml.) for 20 hr. The usual methods isolated a dibasic *acid* (0·3 g.), which formed white crystals, m. p. 174° (Found: C, 67·5; H, 6·7. $C_{18}H_{22}O_5$ requires C, 67·9; H, 6·9%), from ethanol, and a pale yellow viscous liquid (0·3 g.), b. p. 190—206°/0·1 mm. The latter gave a 2 : 4-*dinitrophenylhydrazone* which separated from methanol as orange needles, m. p. 127—128° (Found: C, 60·3; H, 5·3. $C_{21}H_{22}O_6N_4$ requires C, 59·2; H, 5·2%).

We are indebted to the Department of Scientific and Industrial Research for a maintenance grant to one of us, and to the Chemical Society for financial assistance.

WASHINGTON SINGER LABORATORIES,
PRINCE OF WALES ROAD, EXETER.

[*Received, June 23rd,* 1958.]

---

869. 2 : 2′-*Dipyridyl Complexes of Cobalt, Rhodium, and Iridium. Part I. Tervalent Rhodium and Iridium Complexes.*

By B. MARTIN and GWYNETH M. WAIND.

Tris-2 : 2′-dipyridylrhodium(III) and bis-2 : 2′-dipyridyldichlororhodium(III) perchlorates and nitrates and tris-2 : 2′-dipyridyliridium(III) perchlorate have been prepared. The pure solids are all diamagnetic. Ultraviolet and visible absorption spectra of their aqueous solutions are described.

MANY properties of transition-metal complexes can be accounted for by considering the number of *d* electrons in the metal ion and their electrostatic interaction with the field provided by the ligands. This " crystal-field " treatment accounts quantitatively for the visible absorption spectra of some complexes of the first transition series [1,2] and of the second and third transition series.[3] The existence of new and intense absorption bands not characteristic of the metal ion or ligand (" charge-transfer " spectra) indicates that in some cases the ligands are not content with the passive rôles ascribed to them in this treatment and has led to a more satisfactory molecular-orbital treatment (" ligand-field ") [4,5] with the crystal-field and Pauling's hybridisation theory as limiting cases.

Chatt's later experimental work [6] confirmed his suggestion that for complexes containing ligands such as 2 : 2′-dipyridyl which have empty π-type orbitals it is necessary to consider bonds formed from these and filled *d* orbitals of the metal. These π bonds are formed by the three orbitals whose angular dependence (d_{xy}, d_{zx}, d_{yz}) allows their energy to remain unchanged in the crystal-field treatment of *octahedral* complexes. Octahedral trisdipyridyl complexes with six *d* electrons may contain three π bonds; tetraco-ordinated square planar complexes two. It is these π bonds, in addition to the σ bonds, which form the " double bonds " suggested by earlier workers [7] in attempts to explain the anomalously high thermodynamic stability of the diamagnetic trisdipyridyliron(II) cation. The recent

[1] Orgel, *J.*, 1952, 4756.
[2] Moffitt and Balhausen, *Ann. Rev. Phys. Chem.*, 1956, **7**, 107.
[3] Jørgensen, *Acta Chem. Scand.*, 1956, **10**, 500.
[4] Orgel, *J. Chem. Phys.*, 1955, **23**, 1004, 1819, 1824.
[5] Owen, *Proc. Roy. Soc.*, 1955, *A*, **227**, 183.
[6] Chatt, *e.g.*, *J.*, 1955, 4456, and earlier and later papers.
[7] Burstall and Nyholm, *J.*, 1952, 3570.

XUM

preparation [8] of dipyridyl complexes of chromium and vanadium in low valency states seemed to emphasise the importance of two or even one π bond in such complexes. We therefore surmised that a trisdipyridylcobalt(I) cation which could contain three π bonds would be stable and later extended our work to rhodium and iridium.

Trisdipyridylrhodium(III) and trisdipyridyliridium(III) perchlorate and nitrate were prepared as starting materials for the preparation of similar compounds in lower valency states,[9] and so that their properties could be compared with those of the trisdipyridylcobalt(III) cation, whose reduction led to the detection and preparation of the corresponding univalent cobalt complex.[10]

Rhodium(III) compounds containing chlorine and dipyridyl have previously been reported [11] but only one brown solid, $Rh(dipy)_3Cl_3$, has been prepared pure. No dipyridyliridium compounds have been described.

Published procedures of preparation of tervalent rhodium and iridium salts [12,13] are all tedious and analytical methods have been either gravimetric determinations of the metal [14] (requiring large amounts of these expensive elements), or based on colour changes which often depend on the composition of the solutions and the time at which measurements were made. These difficulties arise because the starting materials usually rhodium trichloride and potassium chloroiridite) undergo substitutions and redox reactions *slowly* in aqueous solution. We therefore fused the starting materials with the anhydrous ligand, and determined iridium colorimetrically in oxidised solutions which were rapidly equilibrated by addition of platinum black as catalyst.[16]

Bisdipyridyldichlororhodium(III), trisdipyridylrhodium(III), and trisdipyridyliridium(III) perchlorates have been isolated. They are all diamagnetic, like the cobaltic complex. The formulæ of the rhodium salts were confirmed by measuring the conductivity in nitrobenzene. These results are compared with those for trisdipyridylcobalt(II) perchlorate in Fig. 1. The slopes of the plots for the singly, doubly, and triply charged cations are 185, 570, and 1740 respectively. The extrapolated values of the molar conductivity (Λ_0) show the expected [15] proportionality between mobility and cation charge (n), and are given by Λ (ohm^{-1} cm.^{2}) $= 44{\cdot}8n - 13$. They agree well with those listed (for one concentration) by Harris and Nyholm.[17]

The visible and ultraviolet absorption spectra of trisdipyridyl-rhodium(III) and -iridium(III) perchlorates in aqueous solution are given, together with those of trisdipyridylcobalt(III) perchlorate and of 2 : 2′-dipyridyl in Figs. 2 and 3. The maxima of the absorption bands, their molar extinction coefficients, and the suggested origins of the bands, are given in the Table.

$[Co(dipy)_3](ClO_4)_3$		$[Rh(dipy)_3](ClO_4)_3$		$[Ir(dipy)_3](ClO_4)_3$		
$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{max.}$	$\varepsilon_{max.}$	Type of band
Edge at 260	40,000	240	38,800	257	36,400	1
306	34,800	305	33,800	306	27,600	1
317	31,200	318	31,600	315	27,400	1
				~280	~16,400	2
448	67·9	490	27·1			3
		530	28·2			3

These absorption spectra, and those of other dipyridyl complexes,[18] confirm the earlier suggestions [19] that the absorption bands can be divided into three classes, *viz.*, (1) those

[8] Herzog, *Z. anorg. Chem.*, 1952, **267**, 337; *Naturwiss.*, 1956, **43**, 35.
[9] Waind and Martin, *Proc. Chem. Soc.*, 1958, 169.
[10] Waind and Martin, International Conference on Co-ordination Chemistry, Rome, 1957.
[11] Dwyer, *Chem. Rev.*, 1954, **54**, 1001.
[12] Delépine, see Jørgensen, *Acta Chem. Scand.*, 1957, **11**, 165, for complete references.
[13] Jaeger and van Dijk, *Proc. Acad. Sci. Amsterdam*, 1934, **37**, 284.
[14] Collman and Holtzclaw, *J. Amer. Chem. Soc.*, 1958, **80**, 2054.
[15] Davies, "Conductivity of Solutions," Chapman and Hall, London, 1933, p. 215.
[16] Waind, *Chem. and Ind.*, 1955, 1388.
[17] Harris and Nyholm, *J.*, 1956, 4377.
[18] Waind and Martin, unpublished work.
[19] *E.g.*, Schläfer, *Z. phys. Chem.*, 1956, **8**, 373.

characteristic of the ligands ($\varepsilon \sim 10^4$; ultraviolet), (2) " charge-transfer " or " redox " bands ($\varepsilon \sim 10^3$; ultraviolet or visible), and (3) metal ion (" crystal-field ") bands ($\varepsilon \sim 10^2$; visible or near ultraviolet).

1. *Ligand bands.* These have an irregular vibrational structure indicating strong coupling between electronic and vibrational levels. The highest-energy band of the dipyridyl ligand is displaced to shorter wave-lengths in the order $Rh^{3+} > Co^{3+} > Ir^{3+}$.

FIG. 1. *Electrical conductances of* (*A*) $[Rh(dipy)_2Cl_2]ClO_4$, (*B*) $[Co(dipy)_3](ClO_4)_3$, *and* (*C*) $[Rh(dipy)_3](ClO_4)_3$.

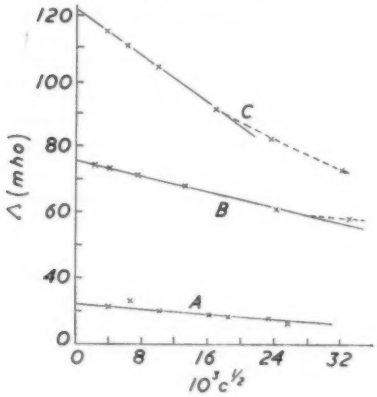


FIG. 2. *Ultraviolet spectra of* (*A*) 2 : 2′-*dipyridyl and* (*B*) *trisdipyridylcobalt*(III), (*C*) *trisdipyridylrhodium*(III), *and* (*D*) *trisdipyridyliridium*(III) *perchlorates.*

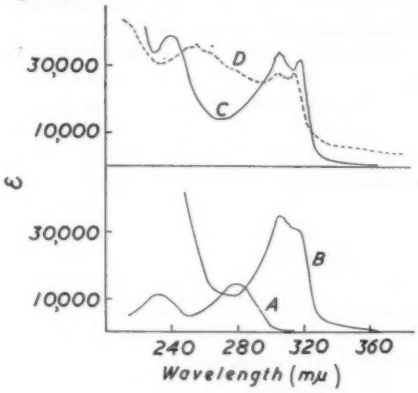
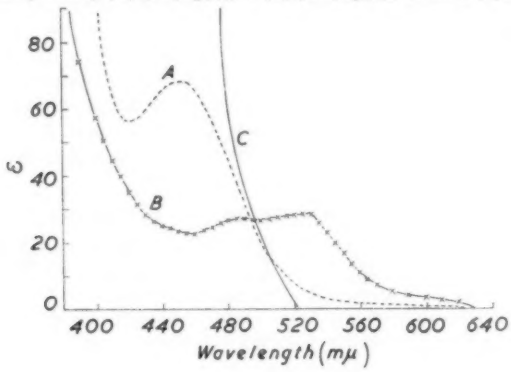


FIG. 3. *Visible spectra of* (*A*) $[Co(dipy)_3]^{3+}$, (*B*) $[Rh(dipy)_3]^{3+}$, *and* (*C*) $[Ir(dipy)_3]^{3+}$.



The second, lower-energy band is split; the position of both subsidiary bands is the same for the three triply charged cations. This agrees with Schlafer's results [19] for the corresponding doubly charged cations.

2. *Charge-transfer bands.* The iridium(III) complex differs from the cobalt(III) and rhodium(III) complexes in that it has a broad band in the ultraviolet region, for which $\varepsilon \sim 5400$ per dipyridyl molecule (cf. $\varepsilon \sim 10{,}000$ per ligand molecule for bands of type 1). This can presumably be attributed to partial electron-transfer from the iridium to the dipyridyl ligands ($Ir^{III} \longrightarrow Ir^{IV}$) and is exactly analogous to the broad band observed by Jørgensen [3] for iridium(III)–pyridine complexes ($\varepsilon \sim 2000$ per pyridine molecule compared with $\varepsilon \sim 4000$ per pyridine molecule in the ligand bands).

XUM

3. *Bands characteristic of the metal ion.* Fig. 3 shows that only the rhodium and cobalt complexes have detectable bands of this type. In both cases they illustrate the surprising success of the crystal-field treatment in predicting the positions and intensities of such bands even when, as here, it can only be an approximation. Thus, for both complexes the bands are broad ($t_{2g}^{(-1)}$,e_g) and correspond to those observed [3] for the aquo-, halogeno-, and oxalato-complexes and classified according to the crystal-field theory as due to transitions to singlet states. However, the expected difficulty in fitting the dipyridyl ligand into any " spectrochemical series " is well illustrated. Thus, for the other ligands listed the position of the longest-wavelength band has been used successfully to investigate the relative intensities of high crystal-field strengths for the series Co^{3+}, Rh^{3+}, Ir^{3+}. It was found that if the hypsochromic shift for any one ligand was taken as 1·00 for Co^{3+} then the corresponding value for Rh^{3+} was 1·54. For the bands in Fig. 3, if Co^{3+} is taken as unity, the corresponding value for Rh^{3+} is 0·85.

Experimental

All solids were vacuum-desiccated over potassium hydroxide.

Materials.—Rhodium trichloride ($RhCl_3,3H_2O$) and potassium chloroiridite ($K_3IrCl_6,3H_2O$) were used as obtained from Messrs. Johnson Matthey and Co. Ltd. All other reagents were " AnalaR."

Tris-2 : 2′-dipyridylrhodium(III) *Perchlorate* $[Rh(dipy)_3](ClO_4)_3$ *and Dichlorobis-2 : 2′-dipyridyldichlororhodium*(III) *Perchlorate* $[Rh(dipy)_2Cl_2](ClO_4)$.—0·20 g. of finely powdered rhodium trichloride trihydrate and 0·78 g. of 2 : 2′-dipyridyl were fused in a test-tube. After expulsion of water the temperature was allowed to rise to the b. p. of dipyridyl (272—273°) and kept thereat for 20 min. during which the reddish-black colour of the rhodium trichloride disappeared leaving a part green, part orange, residue. This was cooled, dissolved in 150 ml. of boiling water, and filtered hot. The filtrate (X) was treated with sodium perchlorate and cooled. The first yellow *precipitate* (Found: C, 41·65; H, 3·23; N, 10·03; Cl, 12·10; ClO_4, 17·09; Rh, 17·0%. $[Rh(dipy)_2Cl_2]ClO_4$ requires C, 41·0; H, 2·7; N, 9·55; Cl, 12·08; ClO_4, 16·96; Rh, 17·54%) was separated pure from the second pink *precipitate* {Found: C, 41·0; H, 3·14; N, 9·76; ClO_4, 34·1; Rh, 11·5%. $[Rh(dipy)_3](ClO_4)_3$ requires C, 41·4; H, 2·8; N, 9·66; ClO_4, 34·3; Rh, 11·8%} by repeated fractional crystallisation. Addition of potassium nitrate instead of sodium perchlorate to the hot filtrate (X) gave crystals of $[Rh(dipy)_2Cl_2]NO_3$. The corresponding $[Rh(dipy)_3(NO_3)_3$ is very soluble and was not isolated from aqueous solution.

Tris-2 : 2′-dipyridyliridium(III) *Perchlorate* $[Ir(dipy)_3](ClO_4)_3$.—0·20 g. of potassium chloroiridite and 0·54 g. of 2 : 2′-dipyridyl were heated, then treated as in the preparation of the analogous rhodium complex. The single *product* was a bright orange powder {Found: C, 36·6; H, 2·5; N, 8·2; ClO_4^-, 31·0; Ir, 20·0%. $[Ir(dipy)_3](ClO_4)_3$ requires C, 37·5; H, 2·5; N, 8·76; ClO_4, 31·1; Ir, 20·12%}.

Tris-2 : 2′-dipyridylcobalt(III) perchlorate trihydrate $[Co(dipy)_3](ClO_4)_3,3H_2O$ and tris-2 : 2′-dipyridylcobalt(II) perchlorate $[Co(dipy)_3](ClO_4)_2$ were prepared as described by Burstall and Nyholm.[7]

Analysis.—Cobalt was determined colorimetrically as its " Nitroso-R salt ".[20] Iridium was determined colorimetrically by a modification of Maynes and Macbryde's method.[21] The final solution was obtained by heating on a steam-bath a solution of the iridium compound in concentrated sulphuric acid with an excess of ceric ammonium sulphate and a suspension of platinum black in water. Addition of the platinum black (which was filtered off before the light absorption of the final solution was measured) reduced the time taken for the solution to reach equilibrium from 10—12 to 1—1½ hr. Rhodium was determined colorimetrically by Ayres and Young's method.[22] Perchlorate was determined gravimetrically as " nitron " perchlorate. Chlorine (other than perchlorate) was determined gravimetrically as silver chloride.

Conductivity Measurements.—The solvent, nitrobenzene, purified by Krauss's method,[23] had

[20] Mellan, " Organic Reagents in Inorganic Chemistry," Blakiston, London, 1951.
[21] Maynes and Macbryde, *Analyst*, 1954, **79**, 234.
[22] Ayres and Young, *Analyt. Chem.*, 1952, **24**, 165.
[23] Krauss, *J. Amer. Chem. Soc.*, 1947, **69**, 2472.

specific conductance $4{\cdot}4 \times 10^{-9}$ mho. All measurements were made at 25° ± 0·01° in a cell with platinised platinum electrodes and the Gambrell A.C. Bridge described by French and Singer.[24] The cell constant was 0·115.

Magnetic Measurements.—Susceptibilities were measured by the Gouy method with an air-cooled electromagnet in a flat-bottomed glass tube of 2 mm. internal diameter.

Spectrophotometric Measurements.—All measurements were made at room temperature with a Unicam S.P. 500 spectrophotometer with 1 cm. matched silica cells.

We thank this College for a research studentship (to B. M.) and Miss C. M. French for the use of the conductivity and magnetic apparatus.

QUEEN MARY COLLEGE (UNIVERSITY OF LONDON),
MILE END ROAD, LONDON, E.1. [*Received, June 25th,* 1958.]

[24] French and Singer, *J.*, 1956, 1424.

---

870. *The Catalytic Hydrogenation of Unsaturated Hydrocarbons. Part II.*[1] *Reaction between Dideuteroacetylene and Hydrogen over a Nickel–Pumice Catalyst.*

By G. C. BOND.

The products of the reaction between dideuteroacetylene and hydrogen over a nickel–pumice catalyst between 40° and 120° have been analysed by mass- and infrared spectrometry. All possible deuterated ethylenes were found, dideuteroethylene always predominating; their relative yields at constant temperature were not markedly dependent on the hydrogen : acetylene ratio, but the proportion of dideuteroethylene fell with increasing temperature. Only about 5% of the dideuteroethylene was in the asymmetric form, but the ratio of the *cis*- to the *trans*-form fell from about 4·0 at 40° to 2·0 at 100°.

A simple theoretical scheme involving only two disposable parameters accounts very satisfactorily for the observed ethylene distributions, including the ratio of asymmetric to symmetric dideuteroethylene. A fraction $s/(1-s)$ measures the chances of any adsorbed acetylene molecule or vinyl radical's gaining a hydrogen atom as against a deuterium atom, and $p/(1-p)$ determines the relative chances of a vinyl radical's becoming ethylene or reverting to acetylene. Values of s are independent of temperature but increase with increasing hydrogen : acetylene ratio, while the reverse is true for values of p. The relevance of the results to the mechanisms suggested in Part I [1] is discussed.

ALTHOUGH deuterium has been widely employed to obtain a better understanding of the mechanisms of olefin hydrogenation and hydrocarbon exchange,[2] it has been little used to study processes involved in the hydrogenation of the acetylenic triple bond. Farkas and Farkas,[3] working with a platinum catalyst at 20°, found that the exchange reaction $C_2H_2 + D_2 \longrightarrow C_2HD + HD$ proceeded to only a negligible extent. Arnett and Crawford [4] attempted the synthesis of *cis*-dideuteroethylene from acetylene and deuterium by means of a palladium catalyst, but obtained all possible deuteroethylenes. The same object caused Douglas and Rabinovitch [5] to study the system in greater detail using a nickel–kieselguhr catalyst. They found that, while acetylene and deuterium interacted at room temperature to give approximately equal yields (20—25% each) of the *cis*- and the *trans*-isomer of dideuteroethylene, lowering the temperature to −80° greatly

[1] Part I, *J.*, 1958, 2705.
[2] See for example Bond, *Quart. Rev.*, 1954, **8**, 279.
[3] Farkas and Farkas, *J. Amer. Chem. Soc.*, 1939, **61**, 3396.
[4] Arnett and Crawford, *J. Chem. Phys.*, 1950, **18**, 118.
[5] Douglas and Rabinovitch, *J. Amer. Chem. Soc.*, 1952, **74**, 2486.

XUM

increased the yield of *cis*-isomer. The use of equilibrated and non-equilibrated hydrogen–deuterium mixtures to effect the reduction resulted in very similar distributions of products.

I have now studied this system further by more careful analysis and over a wider range of conditions. I expected that the results would assist the interpretation of the kinetics found in Part I. Since the preparation of fairly pure dideuteroacetylene is straightforward, I decided to introduce the tracer element into the acetylene rather than the hydrogen.

Experimental

The apparatus and general procedures were as described in Part I,[1] and the same samples of catalyst were used.

Reactants.—Hydrogen and acetylene were treated as before.[1] Dideuteroacetylene was prepared from heavy water (99·7% D_2O) with well-outgassed calcium carbide, by the standard method.[6] The product, analysed mass-spectrometrically, contained 96·0% of C_2D_2 and 4·0% of C_2HD, corresponding to an isotopic purity of 98·0%. Ethylene (British Oxygen Company) and ethane (Chemical Research Laboratory) were outgassed and used to calibrate the mass spectrometer without treatment.

Procedure.—Before each experiment, the catalyst was pretreated with 20—25 mm. of C_2D_2 for not less than 25 min., after which the reaction vessel was pumped for 10 min. The reactants were then admitted, the C_2D_2 being added first (unless otherwise stated), followed by the hydrogen 2 min. later. After the reaction had proceeded to the desired extent, the contents of the reaction vessel were passed through a trap at −196°, where the condensable products were pumped until the unchanged hydrogen had been removed; they were then transferred to a cooled Ward still.[7] An ethylene and ethane fraction (containing a small amount of acetylene) was collected at −183°, and in some experiments the main acetylene fraction was taken at −145°. Mass-spectrometry showed that, unless this distillation technique was used, fragments formed from C_4, C_6, and higher hydrocarbons present in the sample gave rise to ions in the C_2 region, and that these ions seriously interfered with the ethylene–ethane analysis; however at neither of the two distillation temperatures did any detectable amounts of hydrocarbons higher than C_2 distil.

The catalyst was kept under a slight pressure of hydrogen between experiments.

Mass-spectrometry.—The instrument has been fully described;[8] low-energy electrons (nominally 12·7 v, uncorrected for contact potentials) were employed. Average values for the relative positive-ion currents of masses 26—32 (excepting 28) were probably accurate to better than 1%. Mercuric acetate solution was used to remove part of the ethylene from ethylene–ethane mixtures, and the difference between the suitably normalised mass spectra of samples before and after this treatment was therefore the ethylene mass spectrum.

Infrared Analysis.—Selected samples, after distillation, were introduced into a 10 cm. cell having rock-salt plates, and their infrared spectra obtained using a Grubb-Parsons double-beam spectrometer at 25°; cell pressures were 25 mm. or less.

Results

Mass-spectra of Hydrocarbons at Low Voltage.—The use of low-voltage electrons greatly simplifies the mass-spectra of hydrocarbons, as is seen from the annexed figures where a typical mass-spectrum for ethylene at 12·7 v is compared with that recorded in the A.P.I. tables[9] (50 v; in parentheses). At 12·7 v, ions other than the parent are absent from acetylene,[10] and the parent ion $C_2H_4^+$ was formed 3·24 times as readily as the parent ion $C_2H_6^+$ in ethylene–ethane mixtures.

Mass	28	27	26	25	24
Relative ion currents at 12·7 v	100 (100)	4·00 (62·3)	9·71 (61·2)	— (11·5)	— (3·0)

Calculation of Ethylene Compositions.—The principles of calculation are well known. In setting up the simultaneous equations I assumed that the relative probabilities of loss of atoms of

[6] Bond, Sheridan, and Whiffen, *Trans. Faraday Soc.*, 1952, **48**, 715.
[7] Ward, *Ind. Eng. Chem.*, 1938, **10**, 169.
[8] McElcheran, Ph.D. thesis, Leeds, 1954: Dainton and McElcheran, *Trans. Faraday Soc.*, 1955, **51**, 657.
[9] American Petroleum Institute, Project 44, "Tables of Mass Spectral Data."
[10] Field, Franklin, and Lampe, *J. Amer. Chem. Soc.*, 1957, **79**, 2665.

hydrogen and deuterium from all species were equal, and that likewise the probabilities of losing 2H, HD, and 2D were equal. The validity of these assumptions was shown by comparing the observed with the expected (in parentheses) mass-spectrum at 12·7 v of *trans*-dideuteroethylene, a pure sample of which was kindly provided by Professor B. S. Rabinovitch of the University of Washington. The agreement is satisfactory.

Mass	30	29	28	27	26
Obs. (calc.)	100 (100)	3·6 (1·8)	4·2 (3·7)	4·4 (5·8)	0·8 (1·4)

Effect of Variation of Hydrogen Pressure.—A series of experiments was carried out at 97·3° ± 0·2° to determine the effect on the distribution of products of varying the initial hydrogen pressure; a fixed pressure of 36·2 ± 0·8 mm. of C_2D_2 was used, and hydrogen was

TABLE 1. *Effect on distribution of products of varying the initial hydrogen pressure.*

Reaction (%)	Hydrogen pressure (mm.)	C_2D_4	C_2HD_3	$C_2H_2D_2$	C_2H_3D	C_2H_4	Deuterium no.
39 ± 1	38·0	1·5	19·4	60·8	16·3	2·0	2·06
,,	68·2	1·8	16·7	59·1	20·2	2·2	2·00
,,	93·9	1·3	16·8	61·1	19·1	1·7	2·01
,,	180·5	0·9	13·2	65·5	19·1	1·2	1·97
78 ± 3	40·0	2·0	21·7	58·0	15·8	2·5	2·09
,,	69·0	1·9	18·3	58·2	19·3	2·3	2·02
,,	92·5	1·3	16·8	60·2	20·0	1·7	2·00
,,	181·7	1·3	13·2	63·9	20·1	1·6	1·96

always in excess. Samples were extracted after falls in pressure of about 18 and 36 mm., and on the assumption (see Part I) that $-d(C_2D_2)/dt = 0{\cdot}77 \times -\Delta p$, this corresponds to percentage reactions of about 40 and 80%. The results are given in Table 1. The ethylene analysis is quoted as a percentage composition, and the deuterium number represents the mean number of deuterium atoms per ethylene molecule. It being remembered that the C_2D_2 contains 4% of C_2HD (*i.e.*, its deuterium number is 1·96), it follows that the ethylenes as a whole contain less deuterium than if this impurity were absent: this has not been corrected for in the ethylene analyses in Table 1, but the appropriate correction has been applied to the deuterium numbers to facilitate subsequent discussion. Thus in the first analysis in Table 1 the apparent deuterium number is 2·02; addition of 0·04 gives the figure in the final column.

A deuterium number greater than 2 therefore means that there are on average more than two deuterium atoms per ethylene molecule, the excess having necessarily come from the C_2D_2 with the resultant formation of C_2HD: this indicates the occurrence of an *acetylene exchange reaction*. As seen in Table 1, this occurs only when $H_2 : C_2D_2$ is less than about 2·5. A deuterium number within error of 2 indicates either the absence or the balancing of the exchange reactions: evidence bearing on this will be presented later. A necessary corollary of this absence or balancing is that the composition of products should not vary throughout the reaction, and this is borne out by the results. The slight amount of hydrogen exchange occurring at high $H_2 : C_2D_2$ ratios does not produce a significant change in product distribution through the reaction, since the HD formed is diluted in the excess of hydrogen.

An experiment was performed at 97·3° in which the reactants were added in the reverse order, *i.e.*, the hydrogen before the acetylene. Pressures were: hydrogen, 90·8 mm.; C_2D_2, 36·5 mm.: after 77% of reaction, the ethylene analysis gave C_2D_4, 1·4%; C_2HD_3, 14·7%; $C_2H_2D_2$, 63·1%; C_2H_3D, 19·0%; C_2H_4, 1·8%, corresponding to a deuterium number of 1·99. Comparison with Table 1 shows that this analysis does not differ significantly from that obtained when the normal order of addition was used; it is therefore concluded that the order of admission of the reactants does not affect the ethylene distribution.

Two experiments were also performed at the same temperature with larger pressures of both reactants, and the results are given in Table 2. Comparison with those in Table 1 shows that the use of a larger total pressure decreases the yield of $C_2H_2D_2$ and this is chiefly compensated by a higher yield of C_2HD_3. The resulting deuterium numbers are therefore larger than those at the corresponding reactant ratio in Table 1. The higher C_2D_2 pressure therefore effectively eliminates the hydrogen exchange, despite the correspondingly higher hydrogen pressure.

XUM

TABLE 2. *Effect on the distribution of products of varying the initial hydrogen pressure, after 77—78% reaction at 97·5° ± 0·1°.*

Hydrogen pressure (mm.)	Initial pressure of C_2D_2, 100·6 ± 0·6 mm.					
	C_2D_4	C_2HD_3	$C_2H_2D_2$	C_2H_3D	C_2H_4	Deuterium no.
147·7	2·6	21·6	57·4	15·4	3·0	2·09
431·5	1·9	17·3	59·2	19·4	2·3	2·01

Effect of Variation of Acetylene Pressure.—Experiments were carried out at the same temperature with a fixed initial pressure of hydrogen (38 ± 1 mm.) and a variable excess of pressure of C_2D_2; two analyses were again made for each set of conditions, and the results are shown in Table 3. In every case the deuterium number is significantly greater than 2, and increases with

TABLE 3. *Effect on the distribution of products of varying the initial C_2D_2 pressure at 97·3° ± 0·2°.*

Reaction (%)	C_2D_2 pressure (mm.)	C_2D_4	C_2HD_3	$C_2H_2D_2$	C_2H_3D	C_2H_4	Deuterium no.
39 ± ½	72·8	1·9	21·0	61·8	14·2	1·2	2·12
,,	146·5	2·3	22·3	59·0	14·9	1·4	2·13
68 ± 3	74·8	2·1	22·3	60·0	14·3	1·3	2·14
,,	141·3	3·6	24·2	56·0	14·1	2·0	2·17

increasing amount of reaction: thus although the C_2HD formed is diluted in the excess of C_2D_2, the relative rate of the exchange reaction also increases as the $C_2D_2 : H_2$ ratio rises, the latter being the dominant effect. However the change in composition of the product through the reaction is only really significant when the initial $C_2D_2 : H_2$ ratio is about 3·5: here the yields of C_2D_4 and C_2HD_3 rise, while that of $C_2H_2D_2$ falls, as the reaction proceeds.

Effect of Temperature Variation on the Distribution of Products.—The yield of $C_2H_2D_2$ increases with decreasing temperature (Table 4), and this is accompanied by a corresponding decrease in the yield of C_2HD_3, the other products being almost unaffected: as a result, the deuterium number also falls with decreasing temperature. The inference is therefore that below about 95° the hydrogen exchange predominates, whereas above this temperature acetylene exchange predominates.

TABLE 4. *Effect of temperature on distribution of products with 36·4 ± 0·5 mm. of C_2D_2 and 92·2 ± 1·7 mm. of hydrogen (ratio 2·53 ± 0·08), after 39 ± 1% of reaction.*

Temp.	C_2D_4	C_2HD_3	$C_2H_2D_2$	C_2H_3D	C_2H_4	Deuterium no.
58·0°	1·2	9·6	67·3	19·8	2·1	1·92
77·0	1·4	13·0	63·6	19·4	2·6	1·95
97·3	1·3	16·8	61·1	19·1	1·7	2·01
118·0	1·6	18·2	59·6	18·6	2·0	2·03

A further series of experiments was carried out with a larger pressure of C_2D_2, chiefly to obtain sufficient products for infrared analysis, but mass-spectrometric analyses were also performed, and the results are recorded in Table 5. The trend of the results is very similar to that shown in Table 4 because the larger C_2D_2 pressure causes an increase in the yield of C_2HD_3 and a decrease in $C_2H_2D_2$ (Table 2), while the larger hydrogen pressure reverses these effects (Table 1) which therefore almost cancel each other.

TABLE 5. *Effect of temperature on the distribution of products with 100·6 ± 0·6 mm. of C_2D_2 and 500·5 ± 3·5 mm. of hydrogen, after 77—80% of reaction.*

Temp.	C_2D_4	C_2HD_3	$C_2H_2D_2$	C_2H_3D	C_2H_4	Deuterium no.
40·7°	1·3	7·8	70·2	17·8	2·9	1·91
58·0	1·8	10·1	65·6	19·5	3·0	1·92
80·7	1·6	15·9	61·7	18·8	2·0	2·00
97·7	1·9	17·3	59·1	19·4	2·3	2·01

Acetylene Exchange.—The ethylene analyses imply that with initial $H_2 : C_2D_2$ ratios of less than about 2·5 at 97°, there is an overall acetylene exchange reaction leading to the formation of gaseous C_2HD. To confirm this, the acetylene fractions from six runs at 97·3° were analysed mass-spectrometrically; C_2HD constituted between 6 and 8% of the total acetylene in all

cases. After expressing the results in terms of partial pressures, I obtained initial rates of formation of C_2HD, allowing for the removal of the C_2HD originally present. After correction

TABLE 6. *Dependence of the relative rate of formation of* C_2HD *on pressure of* C_2D_2 *at* 97·3°.

Hydrogen pressure (mm.)	C_2D_2 pressure (mm.)	$+d[C_2HD]/dt$ (mm./min.)	$-dP/dt$ (mm./min.)	$\frac{+d[C_2HD]/dt}{-dP/dt}$
68·5	36·0	0·065	1·60	0·04
38·0	74·0	0·060	0·50	0·12
38·0	144·0	0·200	0·55	0·36

for varying initial rates of fall of pressure, the dependence of the relative rate of formation of C_2HD on C_2D_2 pressure was found (Table 6): the rate of formation of C_2HD in the first run of this series may be somewhat depressed by the higher hydrogen pressure. These results can be quite accurately expressed in the form

$$\text{Relative rate of formation of } C_2HD \propto [C_2D_2]^{1\cdot2}$$

Acetylene exchange is therefore of small importance.

Further confirmation of this view was obtained by allowing a mixture of 17·3 mm. of C_2H_2 and 20·3 mm. of C_2D_2 to react with 91·4 mm. of hydrogen at 97·3°, and analysing the products after 40% of reaction. The initial and final compositions of the acetylene fraction were C_2H_2, 46·0 and 45·1; C_2HD, 2·2 and 4·1; C_2D_2, 51·8 and 50·8% respectively. The amount of equilibration between the acetylenes is seen to be very slight, and there is no change in the deuterium number, both results demonstrating the relative unimportance of the acetylene exchange reaction under these conditions. It is known that isotopic exchange occurs between C_2H_2 and C_2D_2 on this catalyst, which is however rapidly poisoned for this reaction by hydrogenation.[6] In the experiment immediately preceding the one described above, a similar mixture was allowed to react in the absence of hydrogen at the same temperature, the catalyst having been pretreated with acetylene to remove adsorbed hydrogen; after 1 hr. the C_2HD content had risen from 2·2% to 4·4%. This catalyst sample had previously been used for some 200 hydrogenations. The presence of hydrogen therefore increases the rate of formation of C_2HD about three-fold.

The composition of the ethylenes obtained from the hydrogenation of the C_2H_2–C_2D_2 mixture was: C_2D_4, 1·1; C_2HD_3, 5·4; $C_2H_2D_2$, 32·8; C_2H_3D, 17·7; C_2H_4, 43·0%, the deuterium number therefore being 1·04.

Reaction of Dideuteroacetylene with Adsorbed Hydrogen.—Acetylene and adsorbed hydrogen immediately formed some ethylene, but no ethane.[1] To discover more about the mechanism of this process, a similar experiment was carried out at 97° with 24·5 mm. of C_2D_2: a sample was taken after 25 min. and analysed in the mass-spectrometer. It consisted chiefly of C_2D_2, and this therefore precluded the estimation of any C_2H_4 which might have been present. However all the possible deuteroethylenes were detected, and they were estimated as C_2D_4, 16; C_2HD_3, 30; $C_2H_2D_2$, 35; C_2H_3D, 19%. Owing to the small quantity of ethylenes formed, this analysis must be regarded as only approximate (±5%), but nevertheless the formation of ethylenes other than that expected from the direct addition of two adsorbed hydrogen atoms to an acetylene molecule has definitely been established.

Determination of the Relative Proportions of the cis-, trans-, *and Asymmetric Isomers of Dideuteroethylene.*—The spectrum of the distilled products of an early run (100·1 mm. of C_2D_2 and 501·2 mm. of hydrogen at 58·0° to 80% conversion) was recorded from 2 to 15 μ at 25 mm., and the frequencies of the principal absorption maxima agreed within the error of measurement with the literature values for the deuterated ethylenes.[4,11] The spectrum of pure *trans*-$C_2H_2D_2$ was also run over the same wavelength range at 12 mm. pressure, and the observed frequencies of the absorption maxima again agreed well with literature values.[11,12]

The bands chosen for use in estimating the relative proportions of the isomers were the ω_7 modes of each species, which are at 726 cm.$^{-1}$ for *trans*-$C_2H_2D_2$, 751 cm.$^{-1}$ for *asym*-$C_2H_2D_2$ and 842 cm.$^{-1}$ for *cis*-$C_2H_2D_2$. In the cases of the *cis*- and *trans*-isomers, contributions from the ethylenes other than $C_2H_2D_2$ appeared to be negligible at these frequencies: percentage transmissions for these bands were therefore taken from the theoretical base line. The 751 cm.$^{-1}$

[11] Charette and de Hemptinne, *Bull. classe sci. Acad. roy. Belg.*, 1951, **37**, 436.
[12] Crawford, Lancaster, and Inskeep, *J. Chem. Phys.*, 1953, **21**, 678.

XUM

band of *asym*-$C_2H_2D_2$ is superimposed on the fine structure of the 726 cm.$^{-1}$ band of the *trans*-isomer, and transmissions were calculated from a line drawn across the base of the peak. Most samples were run both before and after the cell had been filled to atmospheric pressure with dry air: the addition of air always decreased the transmission.

The spectrum of the products of the early run was obtained at several different pressures both in the presence and in the absence of air: plots of the negative logarithm of the transmissions against pressure were then constructed for the three isomers. The basic assumption was then made that the extinction coefficients of the three chosen bands could be taken as equal. This is perhaps more likely to be true than if bands corresponding to differing modes had been employed. The analysis of this early run at once followed from this assumption, and thereafter the interpolation of any observed transmission into the appropriate Beer's law curve yielded the partial pressure of that isomer: a complete analysis was thus readily obtained.

The results are given in Table 7. Analyses of runs performed under similar conditions gave closely concordant results (see runs A-233 and A-235): the yields of the three isomers vary fairly smoothly with variation in temperature, but at 97° they appear to be independent of

TABLE 7. *Dependence of the relative proportions of* cis-, trans-, *and* asym-$C_2H_2D_2$ *on temperature and partial pressure.*

Reaction, 77—80%. Initial $H_2 : C_2D_2$ ratio (excepting run A-234), 4·65 ± 0·40.

Run	Temp.	Hydrogen pressure (mm.)	C_2D_2 pressure (mm.)	Composition of $C_2H_2D_2$ (%)		
				cis	*trans*	*asym*
B-49	40·7	504·0	100·0	77·5	20·6	1·9
A 237	41·7	338·3	74·2	74·2	22·8	3·0
A-202	58·0	501·2	101·1	75·0	22·3	2·7
A-236	80·7	497·2	100·3	67·7	28·2	4·1
A-235	97·7	431·5	101·2	64·6	30·7	4·7
A-233	97·1	453·1	100·3	64·2	30·7	5·1
A-234	97·4	147·7	100·0	63·5	32·5	4·0

partial pressure variation (runs A-233—A-235). At about 41° there is evidence that a lower total pressure gives a slightly lower degree of stereospecificity than a higher one (runs B-49 and A-237). However, while the reproducibility is satisfactory, the absolute values of the proportions of the isomers may be considerably in error: measurements of the transmissions may be inaccurate, for it is known that, at least for other bands of these isomers, the intensity of any one is a function of the concentrations of the other isomers present, and that it also depends on the presence of other ethylenes.[13] Furthermore the assumption concerning the equality of the extinction coefficients is questionable. These points cannot be resolved without full calibrations with the pure components, and it is therefore wise to regard the values in Table 7 as only semi-quantitative: ±7% on the *cis*-, ±3% on the *trans*-, and ±1% on the *asym*-isomer is a conservative estimate of the probable uncertainties.

Nevertheless the qualitative increase in the degree of stereospecificity as the temperature is lowered is beyond question: this is in harmony with Douglas and Rabinovitch's[4] findings although their yield of the *cis*-isomer even at −80° was less than that found at our highest temperatures. The fact that the completely specific production of the *cis*-olefin from acetylene has not yet been found is itself of great interest in view of the reported high stereospecificity often encountered in the reduction of disubstituted acetylenes.[14]

DISCUSSION

There has been no previous attempt to study systematically the mechanism of the catalytic hydrogenation of acetylene by the isotopic tracer technique; however, where comparison is possible, the results of this work are in general agreement with earlier work. Thus, for example, Farkas and Farkas[3] also found that hydrogen-exchange was unimportant in the hydrogenation of acetylene (over a platinum catalyst), and the observation[4] that *cis*-dideuteroethylene is the predominant product of the interaction of acetylene with deuterium over nickel has been confirmed.

[13] Flanagan and Rabinovitch, *J. Phys. Chem.*, 1956, **60**, 724; Rabinovitch, personal communication.
[14] Campbell and Campbell, *Chem. Rev.*, 1942, **31**, 77.

XUM

This work has emphasised the large differences in behaviour between ethylene and acetylene in their hydrogenation over nickel catalysts. In the reaction between ethylene and deuterium, much olefin- and hydrogen-exchange occurs, and their unequal initial occurrence leads to a varying isotopic content of the reactants and hence to changing proportions of deuteroethanes through the reaction.[2] Owing to the greater strength of adsorption of acetylene, the acetylene-exchange process is relatively less important. The reason for the smaller occurrence of hydrogen-exchange finds several possible explanations (see below). However, as the empirical isotopic composition of the ethylene never departs from the stoicheiometrically-expected value by more than about 8%, the distributions of products are generally sensibly constant throughout a reaction. They are not critically dependent upon the initial hydrogen : acetylene ratio used, and it is therefore inferred that the concentrations of adsorbed species are not very sensitive to changes in this ratio, as expected if acetylene is considerably more strongly adsorbed than hydrogen.

Distribution of Deuteroethylenes.—I now attempt a quantitative interpretation of the observed distributions of ethylene in terms of the mechanisms put forward in Part I.[1] There it was suggested that chemisorbed acetylene and hydrogen atoms rapidly interact to form vinyl radicals, which subsequently disproportionate to ethylene and adsorbed acetylene, as

$$2C_2X_3 \longrightarrow C_2X_4 + C_2X_2 \quad \ldots\ldots\ldots\ldots \quad (1)$$

where X represents either H or D. Depending on whether the vinyl radical gaining the X atom is at the time in the normal or the free-radical form,[15] the ethylene formed in this step may be automatically desorbed or may remain adsorbed.[16] If the latter, it may either desorb or suffer further hydrogenation to ethane; it will be assumed that the ratio of the chances of these processes' occurring [9] is independent of the isotopic content of the ethylene. The occurrence of the further hydrogenation of some of the chemisorbed ethylene may therefore be ignored.

The results are interpreted by use of a suitably modified form of the method used by Kemball [17] for the ethylene–deuterium reaction on metal films. No specific mechanism is assumed, but the scheme is consistent with the mechanism outlined above. It is supposed that in the steady state there exist on the surface concentrations a_2, a_1, and a_0 of the acetylenes C_2D_2, C_2HD, and C_2H_2. Each has the same chance (q) of gaining a hydrogen atom and the same chance ($1 - q$) of gaining a deuterium atom: the origin of these atoms is irrelevant. No provision need be made for the desorption of acetylenes. There are equal chances of the addition of the atom to either end of any acetylene. In this manner the six possible vinyl radicals are formed, and each radical has the same chance (p) of gaining another hydrogen atom (chance s) or another deuterium atom (chance $1 - s$) forming ethylene, or of losing a hydrogen or deuterium atom (chance $1 - p$) and reverting to an acetylene. Thus the relative rates of formation of the six ethylenes (*sym*- and *asym*-dideuteroethylene being recognisably different species) are expressible in terms of the parameters a_2, a_1, a_0, s, p, and q, for whose calculation sufficient quantities are in principle known.

However an alternative procedure has been followed. The number of variable parameters has been reduced to two by (i) assuming that the chances of any acetylene or any vinyl radical gaining (say) a hydrogen atom are equal (*viz.*, $s = q$), and (ii) assuming that the ratio $a_2 : a_1 : a_0$ is given with sufficient accuracy by the approximate relationships

$$a_2 : 0{\cdot}5a_2(1 - p)s : 0{\cdot}125a_2(1 - p)^2s^2$$

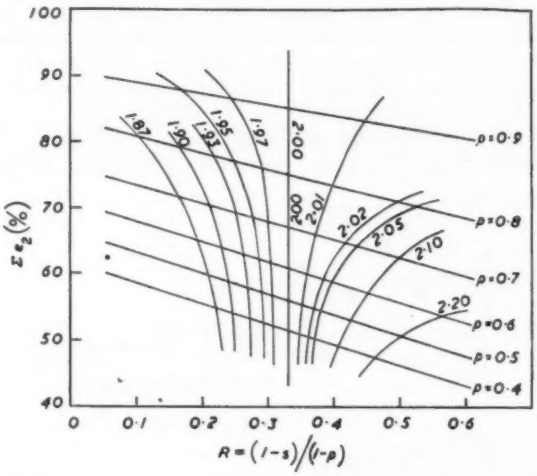
derivable from the theoretical scheme. Some twenty trial calculations were then carried out with various values of s and p. Preliminary indications were encouraging, since the

[15] Sheridan, *J.*, 1945, 133.
[16] Bond, Dowden, and Mackenzie, *Trans. Faraday Soc.*, in the press.
[17] Kemball, *J.*, 1956, 735.

calculations demanded an interdependence between (i) the fraction (α) of dideuteroethylene in the asymmetric form and the total yield of dideuteroethylenes ($\sum e_2$) and (ii) the deuterium number and $\sum e_2$. The senses of these relationships were in harmony with observations.

For the distribution to be symmetrical (*i.e.*, for a deuterium number of 2·00), the relation $R = (1 - s)/(1 - p) = 0{\cdot}33$ has to be obeyed. Deuterium numbers less than

FIG. 1. *Theoretical inter-relationships between Σe_2, R, p, and deuterium number. The near-horizontal lines give the dependence of Σe_2 on R at constant p, while the curves (labelled with the deuterium numbers) give the dependence of Σe_2 on R at constant deuterium number.*



2 result when $R < 0{\cdot}33$, the precise value depending both on R and on the actual values of s and p. Correlating graphs were then drawn, in which the percentage yields of the various deuteroethylenes, α, and the deuterium number were plotted against R at various values of p and against p at various values of R. (Further information concerning the scheme and graphs can be obtained from the author.) The theoretical distribution arising from any pair of values of s and p could then be rapidly obtained by interpolation.

The kind of agreement obtained between calculated and experimental values of the various quantities is shown by three quite typical examples in Table 8. Values of s and p were obtained as follows. Fig. 1 shows the master-graph relating $\sum e_2$, the deuterium number, R, and p: thus for any chosen value of $\sum e_2$ or deuterium number there are an infinite number of conjugate values of R and p, but for every conjugate pair of values of $\sum e_2$ and deuterium number there are unique values of R and p, given by the points of intersection of the lines. Values of R and p were therefore selected by interpolation to

TABLE 8. *Comparison between observed and calculated values of variables.*

Location	s	p	C_2D_4	C_2HD_3	$\sum e_2$	C_2H_3D	C_2H_4	α	$\sum e_1$	Deuterium no.
Table 4, entry 4	—	—	1·6	18·2	59·6	18·6	2·0	—	100	1·99
	0·84	0·57	1·4	18·3	59·5	20·2	1·0	5·5	100·4	2·00
Table 5, entry 1	—	—	1·3	7·8	70·2	17·8	2·9	1·9	100	1·87
	0·88	0·68	0·2	8·0	70·3	20·0	1·3	2·0	99·8	1·85
Table 3, entry 2	—	—	2·3	22·3	59·0	14·9	1·4	—	100	2·09
	0·73	0·62	2·5	21·2	59·0	16·8	1·1	5·5	100·6	2·08

correspond as closely as possible to their observed values. From the value of p, and of s corresponding to R, the remaining five observable variables were independently calculated from the correlating graphs. The five variables are truly independent, since the restriction

that $\sum e_i = 100$ was not imposed: but $\sum e_i$ was always within about 0·5% of 100. However, the value of s is only strictly relevant to the particular isotopic composition of acetylene used in this work. In Table 8 its values were chosen to correspond to the uncorrected rather than the corrected deuterium numbers: they would have been slightly lower had the acetylene been isotopically pure.

In several typical cases the scheme reproduces the experimental results very satisfactorily. Particularly heartening is the agreement between the observed and calculated values of α (rows 3 and 4 in Table 8). Calculated values of α were obtained by the same method for the results given in Tables 2, 5, and 7; they are compared with the observed values in Table 9. The calculations based on values of s and p giving optimum agreement with $\sum e_2$ and deuterium number in the relevant experiment thus reproduce not only the qualitative trend of α with temperature but also the absolute values with gratifying accuracy. This suggests (but does not prove) that the accuracy of the experimental values of α is perhaps greater than was believed.

The values of s and p on which the calculated values of α in Table 9 are based are plotted as a function of temperature in Fig. 2. Now most experiments in Tables 5 and 7 were

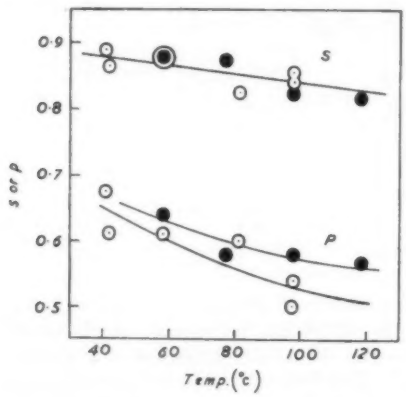


FIG. 2. *Dependence of s (upper curve) and p (lower curve) on temperature.*

○ Initial $H_2 : C_2D_2$ ratio, 4·65 ± 0·35 (Tables 4, 5, and 7).

● Initial $H_2 : C_2D_2$ ratio, 2·5 (Table 4).

performed (A-234 and A-237 are exceptions) with initial acetylene pressures of about 100 mm. and 430—500 mm. of hydrogen. Values of s and p have also been calculated for the results in Table 4 (where the initial hydrogen : acetylene ratio is 2·5) and these also are plotted in Fig. 2. As expected, in both series s is almost independent of increasing

TABLE 9. *Comparison between observed and calculated values of α at various temperatures.*

Run	B-49	A-237	A-202	A-236	A-235	A-233
Temp.	40·7°	41·7°	58·0°	80·7°	97·7°	97·1°
α (obs.)	1·9	3·0	2·7	4·1	4·7	5·1
α (calc.)	2·5	3·2	2·9	4·2	5·6	6·3

temperature while p declines substantially. Hence the activation energy for the conversion of a vinyl radical into ethylene must be less than that for its reversion to acetylene.

Best values of s and p, calculated from Fig. 1 for all results obtained near 97° (Tables 1—5), are plotted against initial hydrogen : acetylene ratio in Fig. 3. Values of s rise smoothly until the reactant ratio is about 2, and thereafter remain constant: values of p show a considerable scatter but may be taken as independent of reactant ratio when this exceeds unity. These trends are in the expected sense. Fig. 1 shows why the scatter of points is greater in the case of p. Of the observable quantities used in determining s and p the deuterium number is probably in error by no more than ±1% while $\sum e_2$ may be uncertain by ±3%. This uncertainty in $\sum e_2$ and no error in the deuterium number

being assumed, p will vary by $\pm 0{\cdot}04$ while s only varies by $\pm 0{\cdot}01$: the " brackets " in Fig. 3 accommodate these uncertainties.

The source of the hydrogen and deuterium atoms used in this treatment must be briefly considered. If it was molecular hydrogen, then s would be unity and *sym*-dideuteroethylene the sole product: if vinyl radicals, then s should be about 0·5. That s is about 0·84 at 100° (Figs. 2 and 3) suggests that atoms come from both sources.

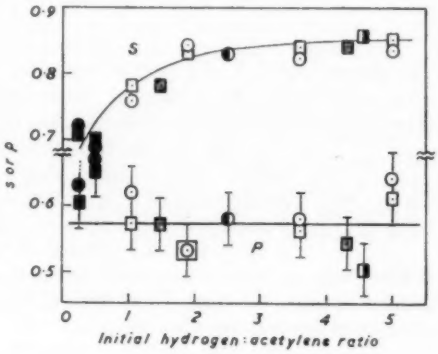


FIG. 3. *Dependence of s (upper curve) and p (lower curve) on initial* $H_2 : C_2D_2$ *ratio at about* 97° C.

Open points, from Table 1; hatched points, from Table 2; full points, from Table 3; ◨, Run A-233 (Table 7); ◐, from Table 4.

Circles refer to measurements made after about 39% of reaction, and squares after about 78% of reaction.

The minor importance of hydrogen-exchange may be partly explained by the low concentration of adsorbed hydrogen and deuterium atoms in the steady state, and partly by the reluctance of vinyl radicals to interact as

$$2C_2X_3 \longrightarrow 2C_2X_2 + X_2 \quad \ldots\ldots\ldots\ldots \quad (2)$$

Such a process may well be more endothermic than the corresponding interaction of adsorbed ethyl radicals.

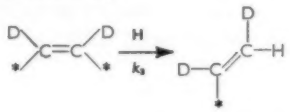
Kemball has suggested [17] that interesting results can be obtained when the precise location of deuterium atoms in hydrocarbon molecules formed in heterogeneous reactions can be determined. Unfortunately considerable rearrangement occurs under electron impact,[18] and mass-spectrometry may be useless in this connection. However in the acetylene system the positional isomers of dideuteroethylene are fairly readily distinguishable by infrared spectroscopy, and the simple theory satisfactorily accounts for their relative abundances. This generalised theoretical approach has considerable merit, and the acetylene system is a promising field in which to test it further.

The relevance of these findings to the mechanisms proposed in Part I must now be considered. The scheme of calculation is consistent with the process whose rate constant was termed k_1: however, no sharp change in the composition of the products has been detected above $P_H°$, and it is therefore concluded that the second mechanism gives rise to deuteroethylenes having essentially the same distribution as those formed through mechanism 1. Mechanism 2 cannot then be simply the direct addition of molecular hydrogen as was suggested in Part I. The dilemma has not been completely resolved, but it is suggested that mechanisms 1 and 2 differ only in that the latter is initiated by *molecular* hydrogen and the former by dissociated hydrogen atoms, and that these two processes may be kinetically independent.

Stereospecificity.—The above procedure makes no attempt to treat the stereochemistry of the addition. Table 7 showed that the stereospecific formation of *cis*-dideuteroethylene was not achieved under any conditions, although the proportion of the *cis*-isomer rose with decreasing temperature, so I must show how both isomers may arise and why the *trans*-isomer may not be formed in more complex acetylenic molecules.[14]

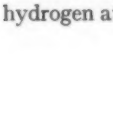
[18] See, for example, McFadden and Wahrhaftig, *J. Amer. Chem. Soc.*, 1956, **78**, 1572.

In the normal form of the vinyl radical, all the atoms (including the metal atom on which it is adsorbed) are coplanar. Now if acetylene is chemisorbed as a *cis*-ethylenic–surface complex, the addition of a hydrogen atom must yield a vinyl radical in which the hydrogen atom is *cis* to the metal atom (3):

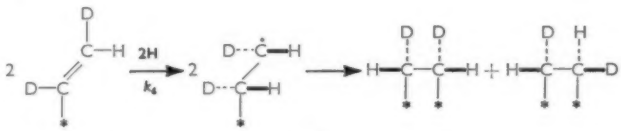


(3)

The simple addition of a further hydrogen atom yielding desorbed ethylene will likewise necessarily lead to the *cis*-isomer. Stereospecificity will be lost as soon as the double-bond is broken, so that if this last process takes the alternative path (4), the ethylenes on desorption will be an equilibrium *cis–trans* mixture if the intermediate free radical survives long enough to allow of free rotation about the C–C bond. Stereospecificity is automatically lost if the vinyl radical assumes the free-radical form (I) since the configuration of atoms about the carbon bearing the odd electron is planar: addition of the hydrogen atom from behind will give adsorbed *trans*-dideuteroethylene, and from in front *cis*. Ethylene formed through the free-radical form of the vinyl radical will therefore be an equilibrium mixture of *cis*- and *trans*-isomers:

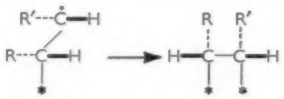


(I)



(4)

Since the free-radical form of the vinyl radical initiates the polymerisation, it is doubtful whether it gives rise to ethylene. If it does not, the degree of stereospecificity is then merely a question of the relative rates at which the carbon–metal bond and the π-bond break when a deuterium atom interacts with a vinyl radical, that is, it is simply a function of k_3/k_4. The results show that $k_3 = k_4$ at about 60° and $E_4 > E_3$.



(5)

Radicals of the type CRH–$\dot{C}$R′H arising from disubstituted acetylenes may be unable to undergo the necessary free rotation owing to interference between R′ and the surface or other adjacent adsorbed molecules. The adsorption would then have to be stereospecific (5), and the *trans*-isomer cannot be formed. The stereospecificity of the hydrogenation of substituted acetylenes is thus logically interpreted.

I thank Dr. K. J. Ivin for assistance with the infrared spectra, Messrs. S. Walker and F. Wilkinson for maintenance of the mass-spectrometer, and the University of Leeds for an I.C.I. Fellowship.

Department of Physical Chemistry,
The University, Leeds, 2.

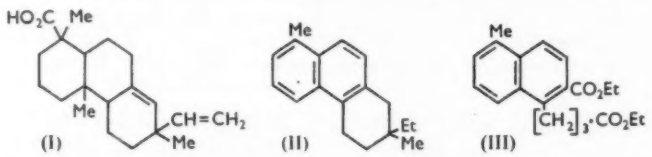
[*Received, June 10th*, 1958.]

871. *Studies in Polycyclic Systems. Part IV.* Synthesis of Some Degradation Products of Dextropimaric Acid and Related Diterpenoids.*

By D. Nasipuri and A. C. Chaudhuri.

The synthesis of two naphthalene derivatives (II and VIII) is described. The former is identical with the trisubstituted naphthalene obtained by partial dehydrogenation [1,2] of dextropimaric acid and related diterpenoids. The latter (VIII) is found to differ, in its trinitrobenzene derivative, from a hydrocarbon derived from the two isomeric dextropimaric acids and to which this formulation was ascribed.[1]

It was shown by Harris and Sanderson [1] that partial dehydrogenation of dextro- or *iso*dextro-pimaric acid (I) with palladium–charcoal gave a trisubstituted naphthalene which they formulated as 2-ethyl-1 : 2 : 3 : 4-tetrahydro-2 : 8-dimethylphenanthrene (II) on the basis of its ultraviolet absorption spectra and further dehydrogenation to pimanthrene. The same hydrocarbon, along with pimanthrene, was also isolated by these workers [2] from the dehydrogenation product of yet another diterpene which they



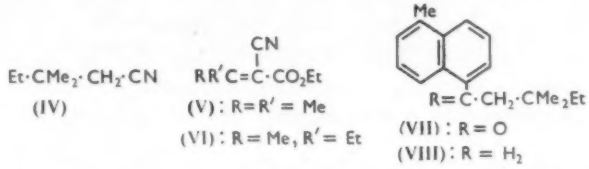
described as *iso*dextropimarinal and identified as cryptopinone (it was, however, established later by Barton, Bruun, and Sörensen [3] that cryptopinone was dextropimarinal). The transformation of these diterpenoids into the hydrocarbon is rather curious [4] and evidently brought about by intramolecular " transfer-hydrogenation " of the vinyl group with partial dehydrogenation of the hydrophenanthrene nucleus. The stability of the hydrocarbon (II) towards further dehydrogenation is expected and recalls the isolation of similar trisubstituted naphthalene derivatives from the dehydrogenation products of methyl totaryl ether.[5] We now confirm the structure of this hydrocarbon by a rational synthesis as follows.

2-Ethyl-1 : 2 : 3 : 4-tetrahydro-8-methyl-1-oxophenanthrene, prepared from ethyl γ-(2-ethoxycarbonyl-5-methyl-1-naphthyl)butyrate [6] (III) by the usual procedure of Dieckmann cyclisation, ethylation, and hydrolysis, was alkylated with methyl iodide in the presence of potassium *tert.*-butoxide, to give 2-ethyl-1 : 2 : 3 : 4-tetrahydro-2 : 8-dimethyl-1-oxophenanthrene. Clemmensen reduction of the latter afforded the desired hydrocarbon (II), the identity of which with the $C_{18}H_{22}$ hydrocarbon derived from the diterpenoids was shown by ultraviolet absorption spectra, a mixed melting point of the trinitrobenzene derivatives, and also by superimposable *X*-ray diffraction patterns and infrared absorption spectra of these derivatives. It appears, therefore, that the two hydrocarbons isolated from dextropimaric acid and *iso*dextropimaric acid are racemic and not the two expected enantiomers differing in the configuration of the quaternary carbon atom. This was also proved by Harris and Sanderson [1] from the absence of optical rotation of the hydrocarbons although the mechanism of racemisation during dehydrogenation is not apparent.

* Part III, Nasipuri, *J.*, 1958, 2734.

[1] Harris and Sanderson, *J. Amer. Chem. Soc.*, 1948, **70**, 2081.
[2] *Idem, ibid.*, p. 3870.
[3] Barton, Bruun, and Sörensen, *Acta Chem. Scand.*, 1951, **5**, 1356; and also Sörensen and Bruun, *Acta Chem. Scand.*, 1947, **1**, 112.
[4] Cf. Harper, *Ann. Reports*, 1948, **45**, 180.
[5] Short and Wang, *J.*, 1951, 2979.
[6] Bardhan and Nasipuri, *J.*, 1956, 350.

Harris and Sanderson also derived a second naphthalene hydrocarbon represented by the structure (VIII), from dextro- and *iso*dextro-pimaric acid [1] through the successive stages of selective hydrogenation of the vinyl group, ozonolysis of the dihydro-acids, Wolff–Kishner reduction, and dehydrogenation. For the synthesis of this hydrocarbon, we condensed 5-methyl-1-naphthylmagnesium bromide [7] with ββ-dimethylvaleronitrile (IV). The latter was obtained by controlled hydrolysis of ethyl 2-cyano-3 : 3-dimethylpentanoate,[8,9] prepared by the action of either (*a*) ethylmagnesium bromide on ethyl 2-cyano-3-methylcrotonate (V) or (*b*) methylmagnesium iodide on ethyl 2-cyano-3-methyl-2-pentenoate (VI). The ketimine hydrochloride, thus formed, was hydrolysed to the ketone (VII) and next converted into the hydrocarbon (VIII) by Martin's modified procedure [10] of Clemmensen reduction. The trinitrobenzene derivative of this hydrocarbon, on crystallisation from ethanol, melted at 113—116° as reported by Harris and Sanderson [1] for their corresponding compound. But on subsequent crystallisations, the melting point rose abruptly and reached a constant value of 141—142°. Reduction of the



ketone (VII) by treatment with a mixture of anhydrous aluminium chloride and lithium aluminium hydride [11] gave the same results. Apparently the trinitrobenzene derivative of this synthetic hydrocarbon differs from that of Harris and Sanderson unless we are dealing with a polymorph. On the other hand, the natural trinitrobenzene derivative might well have been impure as judged from the broad melting range. The ultraviolet absorption curves of the hydrocarbons are similar, having an intense band at 228 mμ, characteristic of disubstituted naphthalenes. No sample, however, was available for comparison.

Two other methods of hydrogenation—use of palladium–charcoal in presence of a trace of perchloric acid,[12] and a mixed catalyst of platinum and palladium [13]—failed to reduced the ketone (VII).

Experimental

2-Ethyl-1 : 2 : 3 : 4-tetrahydro-2 : 8-dimethyl-1-oxophenanthrene.—Ethyl γ-(2-ethoxycarbonyl-5-methyl-1-naphthyl)butyrate (III), m. p. 113°, on Dieckmann cyclisation, ethylation, and hydrolysis as described [6] for analogous cases, gave *2-ethyl-1 : 2 : 3 : 4-tetrahydro-8-methyl-1-oxophenanthrene*, m. p. 120° (Found: C, 85·5; H, 7·7. $C_{17}H_{18}O$ requires C, 85·7; H, 7·6%). The ketone (5 g.) in dry *tert.*-butyl alcohol (30 ml.) was added to a cooled solution of potassium *tert.*-butoxide prepared from potassium (3 g.) and *tert.*-butyl alcohol (60 ml.) under nitrogen. Methyl iodide (15 ml.) was then added and the mixture was stirred at room temperature for 4 hr. and then left overnight. Next day the solvent was evaporated under reduced pressure, and the *product* isolated in the usual way; it crystallised from methanol in leaflets (3·5 g.), m. p. 61—62° (Found: C, 85·4; H, 8·1. $C_{18}H_{20}O$ requires C, 85·7; H, 7·9%).

2-Ethyl-1 : 2 : 3 : 4-tetrahydro-2 : 8-dimethylphenanthrene (II).—The preceding ketone (2 g.) was refluxed with amalgamated zinc (10 g.) and concentrated hydrochloric acid (10 ml.) for

[7] Bardhan, Nasipuri, and Mukherjee, *J.*, 1957, 921.
[8] Prout, *J. Amer. Chem. Soc.*, 1952, **74**, 5915; also Prout, Huang, Hartman, and Korpics, *ibid.*, 1954, **76**, 1911.
[9] Birch, *J.*, 1949, 2721.
[10] Martin, *J. Amer. Chem. Soc.*, 1936, **58**, 1438.
[11] Brown and White, *J.*, 1957, 3755.
[12] Rosenmund and Karg, *Ber.*, 1942, **75**, 1850; Johnson, Christiansen, and Ireland, *J. Amer. Chem. Soc.*, 1957, **79**, 1995.
[13] Koebner and Robinson, *J.*, 1938, 1994.

20 hr. The product on isolation and distillation over sodium in *vacuo* gave the hydrocarbon (II) (1 g.), b. p. 148—150/0·1 mm. (Found: C, 90·6; H, 9·4. Calc. for $C_{18}H_{22}$: C, 90·8; H, 9·2%). The ultraviolet absorption spectra had two intense bands at 232 and 325 mμ. The trinitrobenzene derivative crystallised from ethanol in yellow needles, m. p. 123—123·5° (Found: C, 64·4; H, 5·6; N, 9·5. Calc. for $C_{18}H_{22},C_6H_3O_6N_3$: C, 63·9; H, 5·5; N, 9·3%). It showed no depression in m. p. when mixed with a sample (furnished by Dr. T. F. Sanderson), m. p. 122—123°, derived from the diterpenoids and had identical *X*-ray diffraction patterns and infrared absorption spectra. The hydrocarbon (II) (0·4 g.) was dehydrogenated with 10% palladium–charcoal [14] (20 mg.) to pimanthrene,[15] m. p. and mixed m. p. 86°.

ββ-*Dimethylvaleronitrile* (IV).—Ethyl 2-cyano-3 : 3-dimethylpentanoate, b. p. 115—117°/15 mm., was prepared according to Prout's directions [8] by the action of ethylmagnesium bromide on ethyl α-cyano-β-methylcrotonate [16] (V) and alternatively by the action of methylmagnesium iodide [9] on ethyl 2-cyano-3-methylpent-2-enoate [17] (VI) in approximately the same yield (30%). Hydrolysis of the cyano-ester (18·3 g.) by refluxing a solution in potassium hydroxide (10 g.) and ethylene glycol (30 ml.) for 5 hr. gave the *nitrile* (IV) (9·2 g.), b. p. 164° (Found: C, 75·6; H, 11·8; N, 12·7. $C_7H_{13}N$ requires C, 75·7; H, 11·7; N, 12·6%).

1-*Methyl*-5-ββ-*dimethylvalerylnaphthalene* (VII).—A solution of 1-bromo-5-methylnaphthalene (11·1 g.) in ether (35 ml.) was added dropwise to a suspension of magnesium (2·2 g.) in ether (30 ml.), the reaction being initiated by addition of a few drops of ethyl bromide. Dry thiophen-free benzene (40 ml.) was next added and the mixture gently refluxed on the steam-bath for 4 hr. ββ-Dimethylvaleronitrile (9 g.) in benzene (25 ml.) was gradually dropped in and the whole refluxed for 6 hr., cooled, and poured into ice-water containing concentrated hydrochloric acid (25 ml.). The solvent was removed by steam-distillation and the ketimine hydrochloride (10 g.), m. p. 248—250°, was collected by filtration and dried. It was hydrolysed in refluxing water (60 ml.), concentrated hydrochloric acid (30 ml.), and toluene (35 ml.) for 3 hr. After cooling, the mixture was diluted with water, the organic layer was separated, and the aqueous layer once extracted with benzene. The combined organic extract was washed with water, dried, and evaporated at the water-pump, and the residue was distilled to afford the *ketone* (VII) (9 g.), b. p. 170—172°/1 mm. (Found: C, 84·6; H, 8·8. $C_{18}H_{22}O$ requires C, 85·0; H, 8·7%). It did not give a semicarbazone under ordinary conditions.

Synthesis of the Hydrocarbon (VIII).—(*a*) A mixture of the ketone (VII) (4 g.), amalgamated zinc (20 g.), concentrated hydrochloric acid (35 ml.), water (15 ml.), toluene (20 ml.), and glacial acetic acid (2 ml.) was refluxed for 30 hr. The product was worked up in the usual way and distilled over sodium, to give an oil (2 g.), b. p. 150—152°/2 mm. (Found: C, 89·7; H, 9·9. Calc. for $C_{18}H_{24}$: C, 90·0; H, 10·0%). The trinitrobenzene derivative crystallised from ethanol in yellow needles, m. p. 113—116°; but after several crystallisations, the m. p. rose to a constant value of 141—142° (Found: C, 63·3; H, 5·7; N, 9·5. Calc. for $C_{18}H_{24},C_6H_3O_6N_3$: C, 63·6; H, 6·0; N, 9·3%). Harris and Sanderson [1] record m. p. 113—116°.

(*b*) The ketone (VII) (2 g.) in ether (2 ml.) was slowly added to a cold solution of lithium aluminium hydride (0·52 g.) and anhydrous aluminium chloride (3·7 g.) in dry ether (3 ml.). The mixture was warmed on the steam-bath for 30 min., then cooled, and the excess of the reagent was destroyed by cautious addition of ethyl acetate. The product was taken up in ether, washed with water, and dried, the solvent was removed, and the residue was distilled, to give an oil (1·1 g.), b. p. 152—155°/2 mm. The trinitrobenzene derivative crystallised from ethanol in yellow needles, m. p. 141—142° (Found: C, 63·5; H, 5·8; N, 9·3%).

The authors express their gratitude to Dr. T. F. Sanderson for a gift of the trinitrobenzene derivative of the $C_{18}H_{22}$ hydrocarbon (II), and Mr. A. A. Hock for the determination of *X*-ray diffraction patterns.

UNIVERSITY COLLEGE OF SCIENCE, CALCUTTA-9, INDIA. [*Received, June 26th*, 1958.]

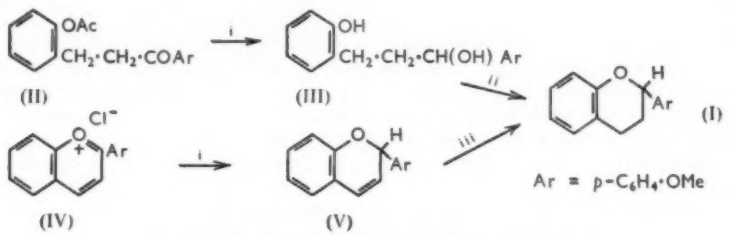
[14] Linstead and Thomas, *J.*, 1940, 1127.
[15] Haworth, Letsky, and Mavin, *J.*, 1932, 1784.
[16] Cope, *J. Amer. Chem. Soc.*, 1937, **59**, 2327.
[17] Cope, Hofmann, Wyckoff, and Hardenbergh, *ibid.*, 1941, **63**, 3452.

872. *Polymerisation of Flavans. Part II.* The Condensation of 4′-Methoxyflavan with Phenols.*

By B. R. Brown and W. Cummings.

4′-Methoxyflavan condenses with phenol or resorcinol in the presence of hydrogen chloride in ethanol, and it has been proved that the heterocyclic ring of the flavan opens in this process. Condensation of 4′-methoxyflavan with 7-hydroxyflavan yields a compound containing two flavan units whose structure is based upon the known *para*-orientation of these reactions.

In Part I * an approach was made towards elucidation of the polymerisation of flavans under the influence of acids. As a result it is known that *p*-hydroxybenzyl alcohols and related compounds condense with phenols preferentially at a position *para* to a hydroxyl group. Also it has been shown [1,2] that benzyl ethers rearrange in the presence of hydrogen chloride to yield diphenylpropanes. Thus the mechanism first advanced by Freudenberg and Maitland [3] for the acid polymerisation of flavans is seen to be plausible, and Freudenberg and de Lama [1] isolated, after reaction of catechin with hydrogen chloride in dioxan, a compound (as its polyacetate) which they claim to be a catechin dimer. By using simpler flavans than catechin it has been our aim to discover whether they condense with phenols in presence of acid, and to synthesise a compound of known structure containing two flavan units.



Reagents: i, $LiAlH_4$; ii, HCl–MeOH; iii, H_2–Raney Ni.

The new compound 4′-methoxyflavan (I) was chosen as the simplest flavan whose heterocyclic ring could be expected to open under the influence of acids. It was prepared by two routes. Reduction of β-*o*-acetoxyphenyl-*p*-methoxypropiophenone (II) with lithium aluminium hydride and ring closure [4] of the resulting alcohol (III) gave the flavan (I) in 61% yield (from salicylaldehyde and *p*-methoxyacetophenone). By reduction of the flavylium chloride (IV) with lithium aluminium hydride and hydrogenation of the flaven (V), an overall yield of 54% (from salicylaldehyde and *p*-methoxybenzaldehyde) has been obtained. In agreement with Elstow and Platt [5] we found this method of flavan synthesis to be superior to the direct hydrogenation of a flavylium chloride,[6] though the hydrogenation of flavylium perchlorates is more satisfactory.[1,7] It is of interest that the flaven (V) has the same melting point (123°) as the compound obtained by Kulkarni and Shah [8] from the hydrogenolysis of 4′-methoxyflavone with lithium aluminium hydride. Although the products of reduction of flavylium salts by lithium aluminium hydride have

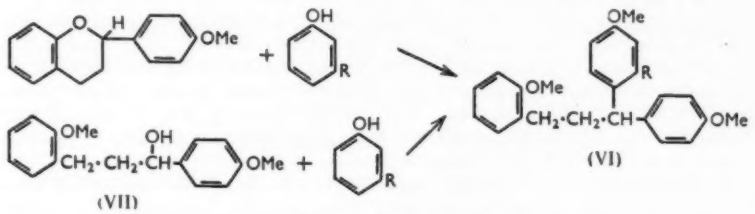
* Part I, *J.*, 1957, 3757.

[1] Freudenberg and de Lama, *Annalen*, 1958, **612**, 78.
[2] von Braun and Reich, *ibid.*, 1925, **445**, 225.
[3] Freudenberg and Maitland, *ibid.*, 1934, **510**, 193.
[4] Harries and Busse, *Ber.*, 1896, **29**, 380.
[5] Elstow and Platt, *Chem. and Ind.*, 1950, 824.
[6] Freudenberg, Stocker, and Porter, *Chem. Ber.*, 1957, **90**, 957.
[7] Brown and Somerfield, unpublished work.
[8] Kulkarni and Shah, *Current Sci.*, 1953, **22**, 339.

XUM

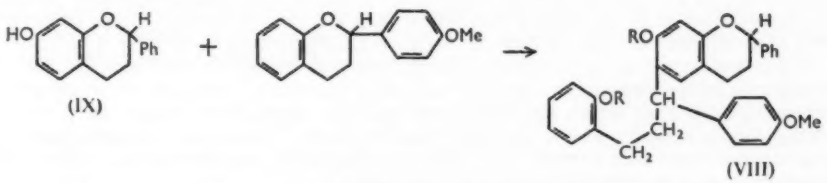
not been rigorously proved to be Δ^3-flavens, this would seem to be the most likely structure.[9,10] Thus Kulkarni and Shah's product may be a Δ^3-flaven, for the migration of double bonds during reduction of αβ-unsaturated ketones with lithium aluminium hydride and aluminium chloride is known to occur in certain circumstances.[11]

Under the influence of hydrogen chloride in ethanol the heterocyclic ring of 4′-methoxyflavan opens and reaction occurs with phenol or resorcinol. After methylation the triarylpropanes (VI; R = H and OMe) were obtained. The alcohol (VII) condenses with phenol to yield, after methylation, a propane (VI; R = H) identical with that resulting from 4′-methoxyflavan and phenol, proving that the oxygen ring of the flavan opens in the reaction. By analogy with previous proved examples [12] it is inferred that the condensation has occurred at a position *para* to a phenolic hydroxyl group.



Reagents: HCl–EtOH, then methyln.

Reaction of 4′-methoxyflavan with a hydroxyflavan whose heterocyclic ring is incapable of fission under the conditions used should yield a compound (VIII), analogous to the catechin dimer of Freudenberg and de Lama,[1] containing two flavan units. To this end 7-hydroxyflavan (IX) has been used and acetylation of the product has yielded a diacetate (VIII; R = Ac). The methoxyl analysis of this compound agrees with that expected for a structure containing two flavan units, and its other structural features follow from the previous condensations.



Under the same conditions 4′-methoxyflavan and flavan itself do not react, presumably because flavan is not sufficiently reactive towards electrophilic reagents of the kind produced by acid fission of the flavan ring.[13]

Experimental

The alumina used was Spence Grade 0; acetic acid was used for deactivation. Light petroleum refers to the fraction of b. p. 30—40° unless otherwise stated.

2 : 4′-*Dimethoxychalcone*.—(*a*) A mixture of *o*-methoxybenzaldehyde (5·0 g.), *p*-methoxyacetophenone (5·5 g.), ethanol (30 ml.), and 10% aqueous sodium hydroxide (6·0 ml.) was kept at room temperature for 1 hr., then diluted with water, and the resulting solid crystallised from ether–light petroleum. The *chalcone* (8·5 g.) separated as pale yellow needles, m. p. 44—45° (Found: C, 76·2; H, 6·1. $C_{17}H_{16}O_3$ requires C, 76·1; H, 5·95%).

[9] Karrer and Seyhan, *Helv. Chim. Acta*, 1950, **33**, 2209.
[10] Freudenberg and Weinges, *Annalen*, 1954, **590**, 140.
[11] Brown *et al.*, unpublished work.
[12] Brown, Cummings, and Somerfield, *J.*, 1957, 3757.
[13] Cf. ref. 10.

(*b*) 2-Hydroxy-4′-methoxychalcone [14] (2·2 g.) was treated with dimethyl sulphate (1·5 ml.) and 10% aqueous sodium hydroxide (4·0 ml.). The chalcone was isolated by means of ether and purified on alumina. Elution with benzene and crystallisation from ether–light petroleum gave pale yellow needles (1·8 g.), m. p. and mixed m. p. 44—45°.

The *dinitrophenylhydrazone* separated from chloroform as orange needles, m. p. 244° (decomp.) (Found: C, 61·75; H, 4·6; N, 12·3. $C_{23}H_{20}O_6N_4$ requires C, 61·6; H, 4·45; N, 12·5%), $\lambda_{max.}$ 4075 Å (log ε 4·56) in chloroform.

p-*Methoxy*-β-o-*methoxyphenylpropiophenone*.—2 : 4′-Dimethoxychalcone (4·15 g.) was hydrogenated in methanol at 20°/764 mm. on Adams catalyst (0·225 g.). The chalcone took up 380 ml. of hydrogen (theor. 370 ml.). Isolation in the usual way gave a colourless oil (3·95 g.) which yielded a *dinitrophenylhydrazone* as brick-red prisms, m. p. 205°, from chloroform–acetone (Found: C, 61·25; H, 4·8; N, 12·35. $C_{23}H_{22}O_6N_4$ requires C, 61·35; H, 4·9; N, 12·45%), $\lambda_{max.}$ 3940 Å (log ε 4·45) in chloroform.

3-o-*Methoxyphenyl*-1-p-*methoxyphenylpropan*-1-*ol* (VII).—The above compound (2·8 g.) was reduced in the usual way with lithium aluminium hydride in ether. The resulting colourless oil (2·8 g.) (whose infrared spectrum in Nujol contained a hydroxyl band at 3400 cm.$^{-1}$) yielded a 3 : 5-*dinitrobenzoate* which separated from acetone–methanol as pale yellow prisms, m. p. 141° (Found: C, 61·5; H, 4·45; N, 6·15. $C_{24}H_{22}O_8N_2$ requires C, 61·8; H, 4·7; N, 6·0%).

4′-*Methoxy*-Δ^3-*flaven* (V).—Dry powdered 4′-methoxyflavylium chloride [15] (hydrated salt, dried *in vacuo* over P_2O_5 for 4 days) (1·5 g.) was added to a slurry of lithium aluminium hydride (1·0 g.) in ether (50 ml.), and the mixture was boiled for 20 min. The complex was decomposed with wet ether, the alumina was washed with ether, and the combined ether extracts were dried and evaporated. Recrystallisation of the residual solid (1·0 g.) from ethanol gave 4′-*methoxy*-Δ^3-*flaven* as needles, m. p. 123° (Found: C, 81·05; H, 5·95. $C_{16}H_{14}O_2$ requires C, 80·7; H, 5·9%).

3-o-*Hydroxyphenyl*-1-p-*methoxyphenylpropan*-1-*ol* (III).—β-*o*-Acetoxyphenyl-*p*-methoxypropiophenone [16] (5·65 g.) was added to a slurry of lithium aluminium hydride (4·4 g.) in ether (250 ml.), and the mixture was boiled for 3 hr. Decomposition in the usual way and evaporation of the ether gave the *alcohol* as a solid (4·74 g.) which separated from aqueous methanol as needles, m. p. 118—119° (Found: C, 74·0; H, 7·15. $C_{16}H_{16}O_3$ requires C, 74·4; H, 6·95%).

4′-*Methoxyflavan* (I).—(*a*) 4′-Methoxyflaven (4·0 g.) in methanol (400 ml.) in presence of Raney nickel (12 g.) took up hydrogen (405 ml.) at 19°/750 mm. (theor. 407 ml.). Filtration and concentration to 20 ml. gave 4′-*methoxyflavan* (3·3 g.) which separated from methanol as plates, m. p. 83—84° (Found: C, 79·8; H, 6·65. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·65%).

(*b*) 3-*o*-Hydroxyphenyl-1-*p*-methoxyphenylpropan-1-ol (2·5 g.) in methanol (50 ml.) and concentrated hydrochloric acid (1·6 ml.) was boiled for 5 min. Addition of water gave 4′-methoxyflavan (2·2 g.) which separated from aqueous methanol as plates, m. p. 83—84°, unchanged on admixture with a specimen from (*a*) above. The ultraviolet spectrum of the flavan in ethanol had max. at 2265 (log ε 4·37), 2750 (log ε 3·60), and 2830 Å (log ε 3·55), and the infrared spectra of the two specimens were identical.

3-o-*Methoxyphenyl*-1 : 1-*di*-p-*methoxyphenylpropane* (VI; R = H).—(*a*) Dry hydrogen chloride was passed for 15 min. into a solution of 4′-methoxyflavan (0·50 g.) and phenol (0·60 g.) in ethanol (20 ml.). After 5 days at room temperature the mixture was poured into water (150 ml.), and the resulting oil isolated in ether. Methylation with dimethyl sulphate and alkali in the usual way yielded an oil which was passed in 2 : 3 v/v benzene–light petroleum (b. p. 40—60°) through alumina. After distillation at 160°/0·05 mm. the *propane* (0·30 g.) separated from light petroleum (b. p. 60—80°) as needles, m. p. 70—71° (Found: C, 79·3; H, 7·4. $C_{24}H_{26}O_3$ requires C, 79·55; H, 7·2%).

(*b*) 3-*o*-Methoxyphenyl-1-*p*-methoxyphenylpropan-1-ol (0·35 g.) was condensed with pheno and worked up as described in (*a*). The colourless oil (0·30 g.) from the column distilled at 170°/0·25 mm. to give a solid which separated from light petroleum as needles, m. p. and mixed m. p. 71—72°. The infrared spectra of the two specimens in Nujol were identical.

1-(2 : 4-*Dimethoxyphenyl*)-3-o-*methoxyphenyl*-1-p-*methoxyphenylpropane* (VI; R = OMe).—With resorcinol 4′-methoxyflavan (1·0 g.) gave the *propane* (1·1 g. after chromatography), b. p. 175°/0·05 mm. (Found: C, 76·15; H, 7·25. $C_{25}H_{28}O_4$ requires C, 76·5; H, 7·15%).

[14] Zwyaer and Kostanecki, *Ber.*, 1908, **41**, 1337.
[15] Kondo and Nakagawa, *J. Pharm. Soc. Japan*, 1930, **50**, 928.
[16] Harford and Hill, *J.*, 1937, 41.

XUM

7-Acetoxy-6-[1-(3-o-aceloxyphenyl-1-p-methoxyphenyl)propyl]flavan (VIII; R = Ac).—Dry hydrogen chloride was passed for 20 min. into a mixture of 4′-methoxyflavan (1·06 g.), 7-hydroxyflavan [17] (1·0 g.), and ethanol (75 ml.). The pale yellow solution was kept at room temperature for 8 days, then poured into water, and the product isolated by using ether. The resulting colourless oil was heated with acetic anhydride (30 ml.) and fused sodium acetate (1·0 g.) for 30 min. and poured into excess of water to yield a solid which was twice put through columns of 10% deactivated alumina and eluted with benzene, the initial eluates in 50% benzene–light petroleum being discarded. The solid *product* (1·35 g.) separated from ether–light petroleum as needles, m. p. 65—66° (Found: C, 76·0; H, 6·3; Ac, 14·65; OMe, 5·3, 5·5. $C_{35}H_{34}O_6$ requires C, 76·35; H, 6·2; 2Ac, 15·65; 1OMe, 5·65%), $\lambda_{max.}$ 2785 (log ε 3·68) and 2845 Å (log ε 3·67) in ethanol.

We thank the D.S.I.R. for a maintenance grant (to W. C.).

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, June 27th*, 1958.]

[17] Robertson, Venkateswarlu, and Whalley, *J.*, 1954, 3137.

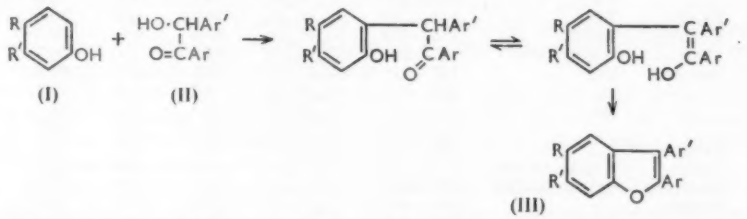
---

873. *The Synthesis of Benzofurans.*

By B. R. BROWN, G. A. SOMERFIELD, and P. D. J. WEITZMAN.

A general synthesis of 3-alkoxyphenylbenzofurans from alkoxybenzoins and phenols has been developed. Variation of the proportions of reactants enables benzo-di- and -tri-furans to be prepared. The structure of the products follows from the mode of synthesis and their ultraviolet spectra.

KNOWLEDGE of the reaction of *p*-methoxybenzyl alcohols with phenols [1] has led to consideration of subsequent condensation of the phenolic hydroxyl group with a second (enolic) hydroxyl group in the alcohol to yield ethers. Thus a compound such as anisoin (II; Ar = Ar′ = *p*-MeO·C_6H_4) would be expected to condense with resorcinol (I; R = H, R′ = OH) to yield a substituted 2 : 3-diphenylbenzofuran (III). Because of the activating groups this reaction should proceed under less vigorous conditions than the condensation [2] of benzoin with phenols in presence of 73% sulphuric acid at 120—160°, and thus enable alkoxybenzofurans to be synthesised in good yield.



(I) (II) (III)

p-Anisoin when boiled under reflux for one hour with an excess of resorcinol and 8% hydrogen chloride in aqueous dioxan has yielded, after methylation, 83% of 6-methoxy-2 : 3-di-*p*-methoxyphenylbenzofuran (III; R = H, R′ = OMe, Ar = Ar′ = *p*-MeO·C_6H_4). It is necessary to use dioxan which is free from peroxides, in order to avoid oxidation of the benzoins to benzils and consequent reduction in yields. Ethanol is not a useful solvent because, in the presence of hydrogen chloride, it reacts with benzoins to yield ethyl ethers.[3]

The method has proved to be a general one for the preparation of substituted benzofurans (see Table). With phenol itself the furan synthesis occurs only to the

[1] Brown, Cummings, and Somerfield, *J.*, 1957, 3757.
[2] Japp and Meldrum, *J.*, 1899, **75**, 1035.
[3] Irvine and McNicoll, *J.*, 1908, **93**, 1601.

extent of 4%, to yield 2 : 3-di-*p*-methoxyphenylbenzofuran (III; R = R′ = H, Ar = Ar′ = *p*-MeO·C_6H_4), because benzyl alcohols condense preferentially with a position *para* to a phenolic hydroxyl group.[1] When the *para*-position is blocked, as with *p*-cresol, the yield of benzofuran is increased. With resorcinol it is possible to omit the methylation and isolate a 6-hydroxybenzofuran (*e.g.*, III; R = H, R′ = OH, Ar = Ar′ = *p*-MeO·C_6H_4), and, with β-naphthol, naphthofurans (IV) are obtained. There is no doubt that other phenols could be used with equal success, but this has not been pursued further in the present work.

Benzoin does not react under the described conditions, but the introduction of a methoxyl group *ortho* or *para* to the alcoholic group leads to easy formation of the benzofuran; for example, from 4′-methoxybenzoin (II; Ar = Ph, Ar′ = *p*-MeO·C_6H_4). The isomer, 4-methoxybenzoin (II; Ar = *p*-MeO·C_6H_4, Ar′ = Ph), with β-naphthol, readily yields the same naphthofuran (IV; Ar = C_6H_5, Ar′ = *p*-MeO·C_6H_4) (mixed melting point and infrared comparison), indicating that, with this benzoin, enolisation occurs

Benzofurans (III), *naphtho*[2, 1-b]*furans* (IV), *benzo*[1, 2-b, 5, 4-b′]*difurans* (V), *and the benzotrifuran* (VII).

No.	Type	R	R′	Ar	Ar′	Yield (%)
1	(III)	H	MeO	*p*-MeO·C_6H_4	*p*-MeO·C_6H_4	83
2	(III)	H	HO	*p*-MeO·C_6H_4	*p*-MeO·C_6H_4	65
3	(III)	H	H	*p*-MeO·C_6H_4	*p*-MeO·C_6H_4	4
4	(III)	Me	H	*p*-MeO·C_6H_4	*p*-MeO·C_6H_4	39
5	(III)	H	MeO	*o*-MeO·C_6H_4	*o*-MeO·C_6H_4	54
6	(III)	H	MeO	Ph	*p*-MeO·C_6H_4	24
7	(III)	H	MeO	3 : 4-CH_2O_2>C_6H_3	3 : 4-CH_2O_2>C_6H_3	38
8	(IV)	—	—	*p*-MeO·C_6H_4	*p*-MeO·C_6H_4	93
9	(IV)	—	—	*o*-MeO·C_6H_4	*o*-MeO·C_6H_4	47
10	(IV)	—	—	Ph	*p*-MeO·C_6H_4	58[a], 68[b]
11	(IV)	—	—	3 : 4-CH_2O_2>C_6H_3	3 : 4-CH_2O_2>C_6H_3	76
12	(V)	H	—	*p*-MeO·C_6H_4	—	47
13	(V)	Me	—	*p*-MeO·C_6H_4	—	52
14	(VI)	Me	—	*p*-MeO·C_6H_4	—	25
15	(VII)	—	—	*p*-MeO·C_6H_4	—	25

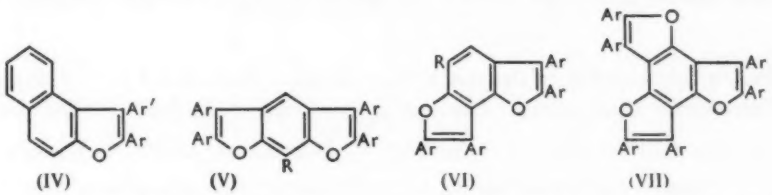
No.	Crystal form	Solvent.*	M. p.	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
1	Needles	Pet[c]	91—92°	$C_{23}H_{20}O_4$	76·8	5·5	76·7	5·55
2	,,	Pet[d]	136—137	$C_{22}H_{18}O_4$	76·1	5·1	76·3	5·2
3	Prisms	Pet[d]	147—148	$C_{22}H_{18}O_3$	79·65	5·55	80·0	5·45
4	Needles	EtOH	122—123	$C_{23}H_{20}O_3$	80·0	6·0	80·2	5·8
5	Prisms	Aq. MeOH	47—49	$C_{23}H_{20}O_4$	76·85	5·8	76·7	5·55
6	Needles	Pet[c]	131—132	$C_{22}H_{18}O_3$	80·3	5·7	80·0	5·45
7	,,	Pet[d]	193—194	$C_{23}H_{16}O_6$	70·7	4·3	71·1	4·1
8	,,	Pet[c]	116—117	$C_{26}H_{20}O_3$	82·1	5·3	82·1	5·3
9	,,	,,	125—126	$C_{26}H_{20}O_3$	82·15	5·0	82·1	5·3
10	Prisms	,,	133—135	$C_{25}H_{18}O_3$	85·9	5·2	85·7	5·1
11	Plates	EtOAc–$COMe_2$	168—169	$C_{26}H_{16}O_5$	76·8	4·05	76·5	3·9
12	Needles	EtOAc–MeOH	221—223	$C_{28}H_{20}O_6$	78·2	5·2	78·35	5·15
13	Prisms	,,	230—231	$C_{29}H_{32}O_6$	78·3	5·4	78·5	5·4
14	,,	Pet[e]	202—203	$C_{29}H_{32}O_6$	78·1	5·6	78·5	5·4
15	Needles	C_6H_6–Pet	340 (dec.)	$C_{54}H_{42}O_9$	77·5	5·0	77·7	5·05

* Pet = light petroleum.
[a] From 4′-methoxybenzoin. [b] From 4-methoxybenzoin. [c] B. p. 40—45°. [d] B. p. 65—70°. [e] B. p. 80—100°.

before reaction. Comparison of the ultraviolet spectra of the benzofurans (*e.g.*, $\lambda_{max.}$ 203, 248, 318 mμ, ε 46,770, 23,710, 26,920 for III; R = H, R′ = OMe, Ar = Ar′ = *p*-MeO·C_6H_4) with that ($\lambda_{max.}$ 233, 318 mμ, ε 21,630, 25,700) of 6-methoxy-2 : 3-diphenylbenzofuran (III; R = H, R′ = OMe, Ar = Ar′ = Ph), prepared by a proved method,[2] confirms the structures deduced from their mechanism of formation.

The use of two mols. of anisoin with one mol. of a resorcinol has enabled benzodifurans (V) to be prepared. These are known to be " linear " compounds from the following considerations. The reaction of anisoin with 2-methylresorcinol must give a " linear "

difuran (V; R = Me, Ar = *p*-MeO·C_6H_4). Conversely, with 4-methylresorcinol an "angular" difuran (VI; R = Me, Ar = *p*-MeO·C_6H_4) is the only one which can be formed. Comparison of the ultraviolet spectra of compounds (V; R = H, Ar = *p*-MeO·C_6H_4), (V; R = Me, Ar = *p*-MeO·C_6H_4), and (VI; R = Me, Ar = *p*-MeO·C_6H_4) leaves no doubt



that the reaction with resorcinol itself leads to the "linear" isomer. This is confirmed by the close similarity between the spectrum of our compound (V; R = H, Ar = *p*-MeO·C_6H_4) and that of the difuran (V; R = H, Ar = Ph) obtained by Japp and Meldrum;[2] the "linear" structure of the latter compound is known from the oxidative degradation carried out by Dischendorfer.[4] The use of phloroglucinol with excess of anisoin yields the trifuran (VII; Ar = *p*-MeO·C_6H_4) which resembles the "angular" difuran in its ultraviolet spectrum.

All the benzofurans prepared exhibit a blue-violet fluorescence in solution, and the "linear" difurans are characterised by a particularly marked fluorescence in the solid state in ordinary light.

Experimental

The light petroleum was of b. p. 40—60° unless otherwise stated. Alumina was Spence Grade O deactivated with 10% acetic acid (10 ml. per 100 g. of alumina). The dioxan was freed from peroxides in the usual way and redistilled from stannous chloride immediately before use.

Monobenzofurans.—The substituted benzoin (1·0 g.), a phenol (3·0 g.), dioxan (30 ml.), and concentrated hydrochloric acid (10 ml.) were mixed and boiled for 1—2 hr. The mixture was poured into water (100 ml.), and the resulting oil taken up in ether.

When monohydric phenols were used this ethereal solution was washed with aqueous sodium hydroxide and water to remove unchanged phenol and other alkali-soluble material, and evaporated. The residue was dissolved in light petroleum–benzene and put on a column of alumina. Elution with light petroleum or light petroleum–benzene yielded the solid benzofuran which was further purified by recrystallisation.

When resorcinol was used the ethereal solution was washed with water and twice with 8% aqueous sodium hydroxide (50 ml.), and the alkaline solution gradually treated with dimethyl sulphate (4 ml.), methylation being completed at 100° for 30 min. The crude product was isolated by using ether and purified on alumina.

For the isolation of 6-hydroxy-2 : 3-di-*p*-methoxyphenylbenzofuran the ethereal solution was washed with water and extracted twice with 8% aqueous sodium hydroxide (50 ml.). The alkaline solution was decolorised by charcoal and acidified, and the crude hydroxybenzofuran isolated in ether. Successive recrystallisation from light petroleum–benzene and from light petroleum (b. p. 60—70°) yielded the pure compound.

Benzodifurans.—Anisoin (1·5 g.), the resorcinol (0·35 g.), dioxan (30 ml.), and concentrated hydrochloric acid (10 ml.) were mixed and boiled for 3 hr. The mixture was poured into water (100 ml.), and the alkali-insoluble *benzofuran* isolated and purified on alumina.

2 : 3 : 5 : 6 : 8 : 9-*Hexa*-p-*methoxyphenylbenzo*[1, 2-*b*, 3, 4-*b'*, 5, 6-*b''*]*trifuran* (*Ring Index No.* 2235) (VII; Ar = *p*-MeO·C_6H_4).–Anisoin (2·0 g.), phloroglucinol (0·35 g.), dioxan (50 ml.), and concentrated hydrochloric acid (10 ml.) were mixed and boiled for 6 hr. The crystalline deposit (0·5 g.) was separated and recrystallised several times from benzene containing a little light petroleum, to give the *benzotrifuran* as colourless needles, m. p. 340° (decomp.). The compound decomposes in light.

[4] Dischendorfer, *Monatsh.*, 1933, **62**, 270.

6-Methoxy-2 : 3-diphenylbenzofuran (III; R = H, R′ = OMe, Ar = Ar′ = Ph).—6-Hydroxy-2 : 3-diphenylbenzofuran [2] was methylated in the usual way. The *product* was purified on alumina and recrystallised from light petroleum (b. p. 60—70°) as prisms, m. p. 123° (Found: C, 84·3; H, 5·7. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·35%).

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, June 27th*, 1958.]

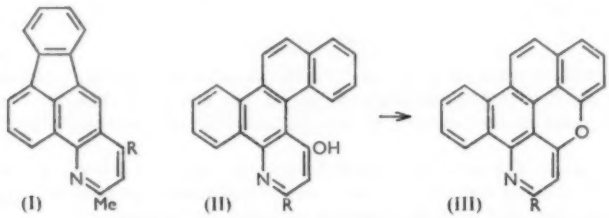
---

874. *Carcinogenic Nitrogen Compounds. Part XXVI.*[1] *Nitrogen-heterocyclic Compounds Derived from Some Polycyclic Arylamines.*

By NG. PH. BUU-HOÏ, G. SAINT-RUF, P. JACQUIGNON, and G. C. BARRETT.

Various cyclisations leading to new nitrogen-heterocyclic systems have been successfully performed with a number of polycyclic arylamines, including 2-aminoanthracene, 3-aminofluoranthene, and 6-aminochrysene; carbostyrils from Conrad–Limpach reactions with 6-aminochrysene give, on zinc dust distillation, always a 4 : 4′-oxygen-bridged compound.

FOR studies of the relations between constitution and carcinogenic and/or carcinostatic activity in polycyclic compounds, condensed nitrogen-heterocyclic compounds have been prepared, starting from arylamines which have activity of these types, *viz.*: 3-aminofluoranthene and 2-aminoanthracene, which are carcinogenic,[2] and 6-aminochrysene, which possesses antitumour activity.[3]



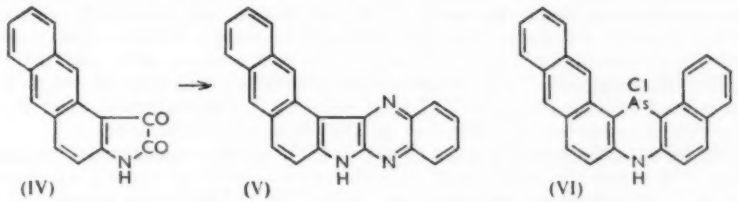
(I) (II) (III)

In the fluoranthene series, the product of the Conrad–Limpach condensation of ethyl acetoacetate with 3-aminofluoranthene [1] was readily converted by zinc dust distillation into 6′-methylpyrido(2′ : 3′-3 : 2)fluoranthene (I; R = H); a homologue (I; R = Me) was obtained by a modified Combes cyclisation [4] of the product of the reaction of acetylacetone with 3-aminofluoranthene. (Incidentally in the preparation of the intermediate 3-nitrofluoranthene,[5] a considerable amount of a dinitrofluoranthene was obtained.) 6-Aminochrysene readily underwent a Conrad–Limpach reaction with ethyl butyryl- or benzoyl-acetate, to give the carbostyrils (II), but these furnished, on zinc dust distillation, 4 : 4′-epoxy-6′-propyl- (III; R = Pr) and 4 : 4′-epoxy-6′-phenyl-pyrido(3′ : 2′-5 : 6)-chrysene (III; R = Ph), in place of the oxygen-free bases.

2-Aminoanthracene readily underwent a Martinet isatin synthesis [6] with ethyl oxomalonate, to give the derivative (IV), and condensation with *o*-phenylenediamine gave the hexacyclic compound (V). Other cyclisations were also successful; thus, 2-(2-naphthylamino)anthracene, prepared by a Knoevenagel reaction [7] of 2-aminoanthracene with β-naphthol, with arsenic trichloride gave the phenarsazine (VI); and a phenothiazine

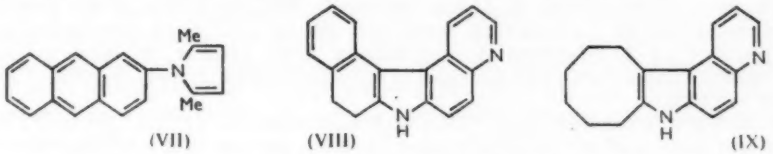
[1] Part XXV, Barrett and Buu-Hoï, *J.*, 1958, 2946.
[2] Schinz, Fritz-Niggli, Campbell, and Schmid, *Oncologia*, 1955, **8**, 233.
[3] Rudali, Buu-Hoï, and Lacassagne, *Compt. rend.*, 1953, **236**, 2020.
[4] Combes, *Compt. rend.*, 1888, **106**, 1536; Buu-Hoï and Guettier, *ibid.*, 1945, **222**, 665; *Rec. Trav. chim.*, 1946, **65**, 502.
[5] Cf. von Braun and Manz, *Annalen*, 1932, **496**, 170.
[6] Martinet, *Ann. Chim.*, 1919, **11**, 15; Buu-Hoï and Hiong-Ki-Wei, *Rev. sci.*, 1944, **82**, 168, 306, 370.
[7] Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 17; Buu-Hoï, *J.*, 1952, 4346.

compound was obtained by condensation with sulphur, although it was not obtained pure. Condensation of 2-aminoanthracene with hexane-2 : 5-dione led to the anthrylpyrrole (VII); with pentane-2 : 4-dione, a monoanil was obtained, but an attempt to cyclise it with sulphuric acid resulted in sulphonation.



(IV) (V) (VI)

In view of the known carcinogenic [8] and carcinostatic properties [9] of : 4-5 : 6-dibenzocarbazole, the similarly built 6 : 7-dihydro-8 : 9-benzopyrido(3′ : 2′-1 : 2)carbazole (VIII) was prepared by a Fischer indolisation of β-tetralone 6-quinolylhydrazone; [10] *cyclo*-



(VII) (VIII) (IX)

octanone 6-quinolylhydrazone similarly gave the indole (IX). This type of compound tends to give very erratic carbon values on analysis.

Experimental

x : 3-*Dinitrofluoranthene*.—Fluoranthene was nitrated at 75—80° in acetic acid, as in the method of Garascia, Fries, and Ching; [11] a 77% yield of 3-nitrofluoranthene was obtained, whose recrystallisation left a by-product (20% yield), which on repeated recrystallisation from acetic acid gave x : 3-*dinitrofluoranthene*, sublimable red needles, m. p. 222° (Found: C, 65·9; H, 2·9. $C_{16}H_8O_4N_2$ requires C, 65·8; H, 2·8%).

6′-*Methylpyrido*(3′ : 2′-2 : 3)*fluoranthene* (I; R = H).—An intimate mixture of 4′-hydroxy-6′-methylpyrido(3′ : 2′-2 : 3)fluoranthene [1] (1 g.) and zinc dust (10 g.) was heated in a Claisen flask, and the solid distillate was recrystallised several times from ethanol, to furnish the *product* as yellow needles, m. p. 177°, giving a yellow halochromy with sulphuric acid (Found: C, 89·5; H, 5·1. $C_{20}H_{13}N$ requires C, 89·9; H, 4·9%). The *picrate* formed lemon-yellow needles, m. p. 245°, from ethanol–benzene (Found: N, 11·5. $C_{26}H_{16}O_7N_4$ requires N, 11·3%).

4′ : 6′-*Dimethylpyrido*(3′ : 2′-2 : 3)*fluoranthene* (I; R = Me).—A solution of the monoanil (1 g.), prepared from 3-aminofluoranthene and pentane-2 : 4-dione,[1] in phosphorus oxychloride (10 c.c.) was refluxed for 2 hr., and on cooling treated cautiously with 10% aqueous sodium hydroxide in excess; the precipitated *base* was collected, washed with water, dried, and recrystallised from ethanol as yellow prisms, m. p. 204° (Found: C, 89·3; H, 5·6. $C_{21}H_{15}N$ requires C, 89·6; H, 5·4%).

4′-*Hydroxy*-6′-*propylpyrido*(3′ : 2′-5 : 6)*chrysene* (II; R = Pr).—A solution of 6-aminochrysene (5 g.) in ethyl butyrylacetate (5 g.) was heated under reflux for 2 hr., whereupon the mixture solidified; the *product* was washed with acetone, and recrystallised from nitrobenzene as colourless prisms (3 g.), m. p. >350°, insoluble in common solvents (Found: C, 85·5; H, 5·5. $C_{24}H_{19}ON$ requires C, 85·4; H, 5·7%).

4 : 4′-*Epoxy*-6′-*propylpyrido*(3′ : 2′-5 : 6)*chrysene* (III; R = Pr).— A mixture of the foregoing compound (2 g.) and zinc powder (20 g.) was dry distilled in the usual way, and the

[8] Boyland and Brues, *Proc. Roy. Soc.*, 1937, **122**, *B*, 429.
[9] Badger, Elson, Haddow, Hewett, and Robinson, *ibid.*, 1942, **130**, *B*, 255.
[10] Cf. Dewar, *J.*, 1944, 616.
[11] Garascia, Fries, and Ching, *J. Org. Chem.*, 1952, **17**, 227.

XUM

distillate was recrystallised several times from ethanol–benzene, giving yellow needles (0·2 g.), m. p. 191° (Found: C, 85·6; H, 5·2. $C_{24}H_{17}ON$ requires C, 85·9; H, 5·1%); the *epoxy-compound* gave a *picrate* as ochre-yellow needles, m. p. 197° (Found: N, 10·0. $C_{30}H_{20}O_8N_4$ requires N, 9·9%).

4 : 4′-*Epoxy*-6′-*phenylpyrido*(3′ : 2′-5 : 6)*chrysene* (III; R = Ph).—6-Aminochrysene (2 g.) and ethyl benzoylacetate (2 g.) was heated at 200° for 20 min., nitrobenzene (5 c.c.) was added to the semi-solid mass, and the mixture was refluxed for a further 30 min. The crude yellow carbostyril (1·5 g.) thus obtained was collected, washed with acetone, dried, and distilled with zinc powder in the usual way. The distilled *product* crystallised as yellow prisms, m. p. 228—229°, from ethanol–benzene (Found: C, 87·5; H, 4·1. $C_{27}H_{15}ON$ requires C, 87·8; H, 4·1%); the picrate formed orange-yellow needles, m. p. 198°, from ethanol–benzene.

4 : 5-*Dihydro*-4 : 5-*dioxoanthra*[2′ : 1′-2 : 3]*pyrrole* (IV).—2-Aminoanthracene was prepared by reduction of 2-aminoanthraquinone (50 g.) with zinc powder (80 g.) and 5% aqueous sodium hydroxide (2 l.); it formed yellow leaflets, m. p. 241° (lit.,[12] 238°), from toluene. 2-Aminoanthracene (1 g.) and ethyl oxomalonate (2 g.) in acetic acid (10 c.c.) were refluxed for 30 min., then poured into water; the crude precipitate was dissolved in 10% aqueous potassium hydroxide, and the solution was boiled for a few minutes, and, on cooling, acidified with hydrochloric acid. The *compound* (IV) formed violet-red needles, m. p. 228—229°, from acetic acid (Found: C, 77·4; H, 3·4. $C_{16}H_9O_2N$ requires C, 77·7; H, 3·5%). When heated with *o*-phenylenediamine (1 g.) in boiling acetic acid (50 c.c.), it (2 g.) gave ***anthra*(2″ : 1″-1′ : 2′)*pyrrolo*(4′ : 5′-2 : 3)*pyrazine*** (V), crystallising from pyridine as brick-red leaflets, m. p. >340°, giving a dark violet halochromy in sulphuric acid (Found: N, 12·8. $C_{22}H_{13}N_3$ requires N, 13·1%).

1-2′-*Anthryl*-2 : 5-*dimethylpyrrole* (VII).—2-Aminoanthracene (2 g.), hexane-2 : 5-dione (5 c.c.), and acetic acid (2 c.c.) were refluxed for 5 hr., and the solid precipitate formed on cooling was collected and recrystallised from acetic acid, giving yellowish prisms, m. p. 160° (Found: C, 88·3; H, 6·1. $C_{20}H_{17}N$ requires C, 88·6; H, 6·3%). Pentane-2 : 4-dione (5 c.c.) with 2-aminoanthracene (2 g.) gave, in similar conditions, ***pentane*-2 : 4-*dione monoanil*** (2 g.), crystallising as yellow prisms, m. p. 196°, from ethanol (Found: C, 82·7; H, 6·5; N, 5·0. $C_{19}H_{17}ON$ requires C, 82·9; H, 6·2; N, 5·0%); an attempt to cyclise this anil with hot sulphuric acid gave only sulphonated resins.

2-2′-*Naphthylaminoanthracene*.—2-Aminoanthracene (2 g.) and β-naphthol (10 g.) were heated with iodine (0·05 g.) for 6 hr. at 200°; after cooling, the solid was pulverised and treated with aqueous sodium hydroxide, and the secondary amine was taken up in benzene and purified by distillation (b. p. ~290°/1 mm.); crystallisation of the distilled *amine* (2 g.) from ethanol gave yellow prisms, m. p. 136—137° (Found: N, 4·4. $C_{24}H_{17}N$ requires N, 4·4%). The *picrate* formed violet needles, m. p. 161°, from benzene (Found: N, 10·5. $C_{30}H_{20}O_7N_4$ requires N, 10·2%).

10-*Chloro*-5 : 10-*dihydro*-1 : 2-*benzonaphtho*(2′ : 3′-8 : 9)*phenarsazine* (VI).—A solution of 2-2′-naphthylaminoanthracene (1 g.) and arsenic trichloride (0·5 g.) in *o*-dichlorobenzene (10 c.c.) was refluxed for 36 hr., then cooled; the precipitate (1 g.) was collected and recrystallised from toluene, to give deep yellow needles of the *phenarsazine*, m. p. 304—305° (decomp. from 290°), giving a violet-red halochromy in sulphuric acid (Found: C, 67·5; H, 3·6. $C_{24}H_{15}NClAs$ requires C, 67·4; H, 3·5%). Condensation of the same secondary amine (1 g.) with sulphur (0·2 g.) in *o*-dichlorobenzene (10 c.c.) in the presence of iodine yielded a thiazine, giving a deep violet halochromy in sulphuric acid.

3 : 4-*Dihydro*-1 : 2-*benzopyrido*(2′ : 3′-8 : 9)*carbazole* (VIII).—6-Quinolylhydrazine dihydrochloride (8 g.), prepared from 6-aminoquinoline according to Wieland and Horner's method,[13] was heated with 2-tetralone (5 g.) and sodium acetate (5 g.) in 30% aqueous ethanol (80 c.c.), and the crude hydrazone was indolised with sulphuric acid (3 c.c.) and acetic acid (20 c.c.) at 100° for 10 min. The *carbazole* (3·5 g.) obtained on basification was crystallised several times from ethanol–acetone, giving yellowish leaflets, m. p. 263° (Found: C, 84·0; H, 5·5; N, 10·0. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2; N, 10·3%). The picrate crystallised as red leaflets, m. p. 298°, from nitrobenzene.

2 : 3-cyclo*Octenopyrido*(3′ : 2′-4 : 5)*indole* (IX).—Prepared as above, from *cyclo*octanone (2·5 g.) and 6-quinolylhydrazine dihydrochloride (2·1 g.), this *indole* (2 g.) formed pale yellow

[12] Ruggli and Henze, *Helv. Chim. Acta*, 1930, **13**, 409.
[13] Wieland and Horner, *Annalen*, 1938, **536**, 89.

needles, m. p. 214° from ethanol (Found: N, 11·2. $C_{17}H_{18}N_2$ requires N, 11·2%); the picrate formed orange needles, m. p. 274°, from ethanol.

This investigation was supported in part by a research grant from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service. The authors thank the authorities concerned, and the Centre National de la Recherche Scientifique of the French Government for a maintenance grant (to G. C. B.).

THE RADIUM INSTITUTE, THE UNIVERSITY OF PARIS. [*Received, June 19th*, 1958.]

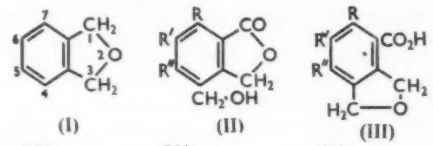
---

875. *Phthalans. Part II.* Ultraviolet and Infrared Spectra.*

By W. R. ALLISON, W. R. LOGAN, G. T. NEWBOLD, and T. J. ROSS.

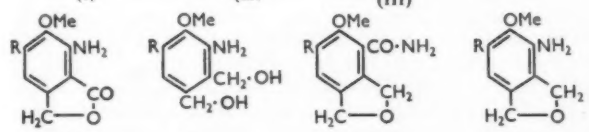
Some new phthalans are described and aspects of the ultraviolet and infrared spectra of these and known members are discussed. An infrared band assignment characteristic of the phthalan ring is put forward.

APART from the parent phthalan (I), which has been prepared by the action of alkali on *o*-xylylene bromide [1] and by pyrolysis of *o*-xylylene glycol,[2] members of this series without substituents in the 1- or 3-position were unavailable until the discovery of the isomerisation of 4-hydroxymethylphthalides to phthalan-4-carboxylic acids, *e.g.*, (IIa) to (IIIa).[3-7] This paper discusses the ultraviolet and infrared spectra of these compounds and others derived from them.



(I) (II) (III)

	R	R′	R″
a:	OMe	OMe	H
b:	OMe	Me	H
c:	OMe	OMe	Me
d:	OMe	OMe	OMe
e:	OMe	H	OMe



(IV) (V) (VI) (VII)

a: R = OMe
b: R = Me

Ultraviolet spectra of 4-hydroxymethylphthalides were compared with those of the corresponding phthalan-4-carboxylic acids in five cases. The isomerisation showed no significant consistent trend in the wavelength positions of maxima or in the intensity of the long-wavelength band or of the middle band where present. It was notable, however, that the low-wavelength band (212—221 mμ) showed a marked decrease in intensity ($\Delta\varepsilon$ 5—15 × 10^3) on passing from the phthalide derivative to the isomeric phthalan while the wavelength position did not exhibit a consistent trend: (IIa) 214 ⟶ (IIIa) 213, $\Delta\varepsilon = -8400$;[3] (IIb) 212 ⟶ (IIIb) 214, $\Delta\varepsilon - 15{,}000$;[5,8] (IIc) 214 ⟶ (IIIc) 212, $\Delta\varepsilon - 12{,}000$;[4] (IId) 218 ⟶ (IIId) 216, $\Delta\varepsilon - 5200$;[4] and (IIe) 221 ⟶ (IIIe) 216 mμ, $\Delta\varepsilon - 9000$.[6]

In order to ascertain the effect of ring closure of an *o*-bishydroxymethylbenzene to a

* Part I, *J.*, 1958, 304.

[1] Willstätter and Veraguth, *Ber.*, 1907, **40**, 965.
[2] Entel, Ruof, and Howard, *J. Amer. Chem. Soc.*, 1952, **74**, 441.
[3] Brown and Newbold, *J.*, 1952, 4878.
[4] Blair and Newbold, *J.*, 1954, 3935.
[5] Blair, Logan, and Newbold, *J.*, 1956, 2443.
[6] Logan and Newbold, *J.*, 1957, 1946.
[7] Blair, Logan, and Newbold, *J.*, 1958, 304.
[8] Brown and Newbold, *J.*, 1953, 1285.

XUM

phthalan upon the ultraviolet spectrum two corresponding pairs of compounds were prepared. The amino-dimethoxy-dialcohol (Va) and the amino-methoxy-methyl-dialcohol (Vb) were prepared by reduction of the corresponding phthalides (IVa) [9] and (IVb) [4] with lithium aluminium hydride. No hydrogenolysis of the alcohol group *ortho* to the amino-group was noted in either reduction.[7,10] 4-Amino-5 : 6-dimethoxyphthalan (VIIa) was prepared by conversion of 5 : 6-dimethoxyphthalan-4-carboxylic acid (IIIa) by way of the acid chloride into the amide (VIa), followed by Hofmann degradation. The aminophthalan (VIIa) was unaffected by hot dilute acid under conditions which converted 5 : 6-dimethoxyphthalan-4-carboxylic acid (IIIa) into 4-hydroxymethylmeconin (IIa). 5-Methoxy-6-methylphthalan-4-carboxylic acid (IIIb) was transformed in a similar way without isolation of the acid chloride into the amide (VIb), and hence into 4-amino-5-methoxy-6-methylphthalan (VIIb). A comparison between the ultraviolet spectra of the amino-alcohols (V) and the corresponding aminophthalans (VII) shows that a hypsochromic shift occurs in the long-wavelength band on ring closure from the alcohol to the phthalan, together with a fall in intensity, *i.e.*, (Va) ⟶ (VIIa) $\Delta m\mu - 8$, $\Delta\varepsilon - 1450$ and (Vb) ⟶ (VIIb) $\Delta m\mu - 15$, $\Delta\varepsilon - 1000$.

The infrared spectra of thirteen phthalans prepared in this Department have been examined, together with those of phthalan and tetrahydrophthalan,[2] for a band which might be characteristic of the phthalan ring. As a result, a band at 910—900 cm.$^{-1}$, usually narrow and of medium strength, has been assigned to this structural unit. This band is comparable with the symmetrical ring-stretching vibration at 913 cm.$^{-1}$ shown by tetrahydrofuran.[11] The stronger asymmetrical ring-stretching vibration shown by tetrahydrofuran at 1098—1075 cm.$^{-1}$ was not characteristic in the phthalan spectra. The assignments are given in the Table. Two examples in the Table need comment: 5 : 6-dimethoxyphthalan-4-carboxyl chloride shows a normal band in Nujol mull but this is 21

Infrared bands of phthalans in the 11 μ *region.*

Substituents in (I)				Max. (cm.$^{-1}$) (in Nujol)	Max. (cm.$^{-1}$) (in CCl_4)	*Substituents in* (I)				Max. (cm.$^{-1}$) (in Nujol)	Max. (cm.$^{-1}$) (in CCl_4)
4	5	6	7			4	5	6	7		
H	H	H	H [3]	904 *	—	$CO{\cdot}NH_2$	OMe	Me	H	905	907
CO_2H	H	H	H	904	—	NH_2	OMe	Me	H	891, 894	906
CO_2H	OMe	OMe	H	906, 900 †	909	CO_2H	OMe	H	OMe	904	908
COCl	OMe	OMe	H	902	881	CO_2Me	OMe	H	OMe	902	907
CO_2Me	OMe	OMe	H	901, 909	910	CO_2H	OMe	OMe	OMe	905	909
$CO{\cdot}NH_2$	OMe	OMe	H	906	907	CO_2H	OMe	OMe	Me	906	911
NH_2	OMe	OMe	H	902	906	Hexahydrophthalan [3]				904 *	—
CO_2H	OMe	Me	H	909	907						

* Medium not specified; frequency estimated from published curves in ref. 2. † Inflexion.

cm.$^{-1}$ less in solution, while 4-amino-5-methoxy-6-methylphthalan shows a normal value in solution with a doublet at a lower frequency in Nujol mull. A phthalan suspected of being substituted in the benzene ring should therefore be examined in both media before a conclusion is drawn. In order to test the specificity of the assignment the positions of bands (Nujol mull in cm.$^{-1}$) between 950 and 850 cm.$^{-1}$ in a number of related compounds are given: 4-hydroxymethyl derivatives of meconin (923 w, 880 m, 871 m), 7-methoxy-6-methylphthalide (918 w, 896 w, 883 w), 5 : 6 : 7-trimethoxyphthalide (897 w), 6 : 7-dimethoxy-5-methylphthalide (871 w), 5 : 7-dimethoxyphthalide (882 w); the 3 : 4- (942 w, 922 w, 853 m) and 4 : 5-dimethoxy- (877 m), 4-methoxy-5-methyl- (895 m), 3-amino-4 : 5-dimethoxy- (946 w), 3-amino- (897 m broad), and 3-amino-4-methoxy-5-methyl- (935 w, 833 m) derivative of *o*-bishydroxymethylbenzene. Other compounds examined were

[9] McRae, VanOrder, Griffiths, and Habgood, *Canad. J. Chem.*, 1951, **29**, 282.
[10] Conover and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 3586.
[11] Jones and Sandorfy in "Technique of Organic Chemistry," Ed. Weissberger, Interscience, New York, 1956, Vol. IX, p. 437; Barrow and Searles, *J. Amer. Chem. Soc.*, 1953, **75**, 1175.

m-dioxano(4′ : 5′-6 : 7)phthalide (887 m in CCl_4), 2-aminobenzyl alcohol (932 m), 3-amino-2-methylbenzyl alcohol (904 m broad). 2-Methylbenzyl alcohol shows no band in this region.[2]

Experimental

Infrared spectra were measured on a Grubb–Parsons S4 spectrometer with sodium chloride optics. Accuracy in the 11 μ region was checked by frequent reference to the 11·038 μ band [12] of polystyrene film. Light petroleum, where used, had b. p. 60—80°.

5 : 6-*Dimethoxyphthalan*-4-*carboxyl Chloride*.—5 : 6-Dimethoxyphthalan-4-carboxylic acid [3] (1·0 g.) was refluxed on the steam-bath for 1 hr. with thionyl chloride (5 c.c.), and the excess of thionyl chloride distilled off under reduced pressure. After being kept overnight *in vacuo* over sodium hydroxide the solid residue was crystallised from benzene–light petroleum (charcoal) to give the *acid chloride* (500 mg.) as blades, m. p. 102·5—103·5° (Found: C, 54·7; H, 4·6. $C_{11}H_{11}O_4Cl$ requires C, 54·4; H, 4·5%).

5 : 6-*Dimethoxyphthalan*-4-*carboxyamide*.—The crude acid chloride from the acid (1·0 g.) was treated in dry ether (20 c.c.) with liquid ammonia (50 c.c.) in portions. The solution was allowed to evaporate overnight; water (50 c.c.) was added to the residue and the mixture extracted with chloroform (3 × 50 c.c.). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue crystallised from chloroform–light petroleum, to give the *amide* (600 mg.) as needles, m. p. 134—135° (Found: C, 59·2; H, 5·9; N, 6·6. $C_{11}H_{13}O_4N$ requires C, 59·1; H, 5·7; N, 6·3%), $\lambda_{max.}$ 209 (ε 27,000) and 308 mμ (ε 3300) in EtOH. The amide sublimes at 130°/10^{-4} mm. Infrared absorption bands in Nujol were at 3413, 3175 (NH_2), and 1669 cm.$^{-1}$ (CO).

4-*Amino*-5 : 6-*dimethoxyphthalan*.—Finely powdered 5 : 6-dimethoxyphthalan-4-carboxyamide (740 mg.) was added at 0° to a portion (10 c.c.) of the hypobromite solution prepared by the addition of bromine (2·05 c.c.) to a stirred ice-cold 10% solution of potassium hydroxide (100 c.c.). After 20 min. at room temperature, the solution was heated to 80° (bath-temperature) for 15 min. The cooled solution was extracted with ether (3 × 25 c.c.) and the combined ethereal extracts were washed with 5% hydrochloric acid (2 × 50 c.c.). Basification of the acid washings with 10% aqueous sodium hydroxide, followed by isolation using ether and crystallisation from benzene–light petroleum, gave 4-*amino*-5 : 6-*dimethoxyphthalan* (500 mg.) as plates, m. p. 96—97·5° (Found: C, 61·5; H, 6·4. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 6·7%). $\lambda_{max.}$ in EtOH 212 (ε 39,300), 240 (ε 8450), and 284 mμ (ε 1400). Infrared absorption bands in Nujol were at 3413, 3333, and 3195 cm.$^{-1}$ (NH_2). The aminophthalan (200 mg.) was refluxed with 3N-hydrochloric acid (5 c.c.) for 2½ hr. The cooled solution was basified, and the product isolated in ether and crystallised from benzene–light petroleum to give unchanged material as plates, m. p. and mixed m. p. 96—97·5° (160 mg.).

5-*Methoxy*-6-*methylphthalan*-4-*carboxyamide*.—5-Methoxy-6-methylphthalan-4-carboxylic acid [5] (1·1 g.) was converted into the amide as described above. 5-*Methoxy*-6-*methylphthalan*-4-*carboxyamide* (0·75 g.) separated from ethanol (charcoal) as prismatic needles, m. p. 174—176° (Found: C, 63·75; H, 6·1. $C_{11}H_{13}O_3N$ requires C, 63·75; H, 6·3%), $\lambda_{max.}$ 209·5 (ε 22,500), and 295 (ε 2300), inflexion at 238 mμ (ε 5600), in EtOH, $\nu_{max.}$ in Nujol 3401, 3175 (NH_2) and 1664 cm.$^{-1}$ (CO).

4 *Amino*-5-*methoxy*-6-*methylphthalan*.—By method used for the preparation of 4-amino-5 : 6-dimethoxyphthalan, 5-methoxy-6-methylphthalan-4-carboxyamide (514 mg.) gave the corresponding *amino-compound* (190 mg.), crystallising from light petroleum as needles, m. p. 74—76° (Found: C, 67·15; H, 7·3. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3%), $\lambda_{max.}$ in EtOH, 213 (ε 40,000) and 276 mμ (ε 1000), $\nu_{max.}$ in Nujol 3420, 3330, and 3236 cm.$^{-1}$ (NH_2).

Methyl 5 : 7-*Dimethoxyphthalan*-4-*carboxylate*.—5 : 7-Dimethoxyphthalan-4-carboxylic acid [6] was esterified in methanol by ethereal diazomethane, to give the *methyl ester*, needles, m. p. 150—151° (from methanol) (Found: C, 60·2; H, 6·0. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%), $\lambda_{max.}$ 218 (ε 23,700), 257 (ε 11,500), and 300 mμ (ε 5300) in EtOH.

1 : 2-*Bishydroxymethyl*-4-*methoxy*-5-*methylbenzene*.—To a boiling partial solution of lithium aluminium hydride (0·83 g.) in ether (140 c.c.) a solution of 6-methoxy-5-methylphthalide (1·38 g.) in tetrahydrofuran (50 c.c.) was added dropwise with stirring. After 2½ hours' refluxing the mixture was cooled to 0° and the excess of hydride decomposed by ice. The

[12] Plyer and Peters, *J. Res. Nat. Bur. Stand.*, 1950, **45**, 462.

mixture was made alkaline with 10% sodium hydroxide solution (60 c.c.), and the ethereal layer separated. The aqueous layer was extracted with ether (5 × 60 c.c.). The combined ether extracts were washed with water, dried (Na_2SO_4), and evaporated. Crystallisation of the residue from benzene–light petroleum gave **1 : 2-*bishydroxymethyl*-4-*methoxy*-5-*methylbenzene*** (1·1 g.), m. p. 71·5—72·5° (Found: C, 66·2; H, 7·7. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%), $\lambda_{max.}$ 209 (ε 12,200), 231 (ε 9150), and 280 mμ (ε 1850) in EtOH.

3-*Amino*-1 : 2-*bishydroxymethyl*-4-*methoxy*-5-*methylbenzene*.—7-Amino-6-methoxy-5-methylphthalide [4] (2·0 g.) was reduced with lithium aluminium hydride (1·2 g.), as described in the preceding experiment, to the *alcohol* (1·2 g.) which separated from benzene–light petroleum as rosettes of needles, m. p. 119° (Found: C, 60·9; H, 7·5. $C_{10}H_{15}O_3N$ requires C, 60·9; H, 7·7%), $\lambda_{max.}$ 219 (ε 43,400) and 291 mμ (ε 2000) in EtOH. The OON-*triacetyl derivative*, formed by the action of acetic anhydride and pyridine on the steam-bath for ½ hr., crystallised from benzene–light petroleum as needles, m. p. 167—168° (Found: C, 59·9; H, 6·9. $C_{16}H_{21}O_6N$ requires C, 59·4; H, 6·55%), $\lambda_{max.}$ 207 (ε 36,800) and 273·5 (ε 760), infl. 230 mμ (ε 10,300) in EtOH.

3-*Amino*-1 : 2-*bishydroxymethyl*-4 : 5-*dimethoxybenzene*.—7-Amino-*m*-meconin [5] (1·0 g.) was reduced, as in the preceding experiment, to the alcohol (750 mg.) which separated from acetone–light petroleum as prismatic needles, m. p. 112° (Found: C, 56·25; H, 7·0. $C_{10}H_{15}O_4N$ requires C, 56·3; H, 7·1%), $\lambda_{max.}$ 213 (ε 39,800), 292 (ε 2850), infl. 238 mμ (ε 6600) in EtOH.

We thank the Department of Scientific and Industrial Research for an Award (to W. R. A.).

THE ROYAL COLLEGE OF SCIENCE AND TECHNOLOGY,
GLASGOW.

[*Received, July 11th,* 1958.]

---

876. π-cyclo*Pentadienylrhenium Carbonyl Compounds.*

By M. L. H. GREEN and G. WILKINSON.

The infrared and high-resolution nuclear magnetic resonance spectra of the compound $C_{10}H_{11}Re(CO)_2$, together with its chemical properties and hydrogenation to $C_{10}H_{13}Re(CO)_2$, have shown that it must be formulated as π-*cyclo*pentadienyl*cyclo*pentadienerhenium dicarbonyl.

π-*cyclo*Pentadienylrhenium tricarbonyl has also been prepared.

DI-π-*cyclo*PENTADIENYLRHENIUM HYDRIDE [1] with carbon monoxide at 100°/250 atm. gives pale yellow crystals of $C_{10}H_{11}Re(CO)_2$ (*A*), first reported by Fischer and Wirzmüller [2] who suggested a structure (I) in which both a π-*cyclo*pentadienyl and a σ-*cyclo*pentadienyl ring were bound to the metal atom and that the additional proton was located between the metal atom and the π-*cyclo*pentadienyl ring as in the structure suggested by Liehr [3] for the di-π-*cyclo*pentadienylrhenium hydride. No physical measurement other than the dipole moment (3·85 D) was reported to support this formulation, but it was noted that the compound showed no acid or base character of the type shown by other transition-metal complex hydrides (cf. ref. 1). Our examination has shown that a different formulation (II) is necessary.

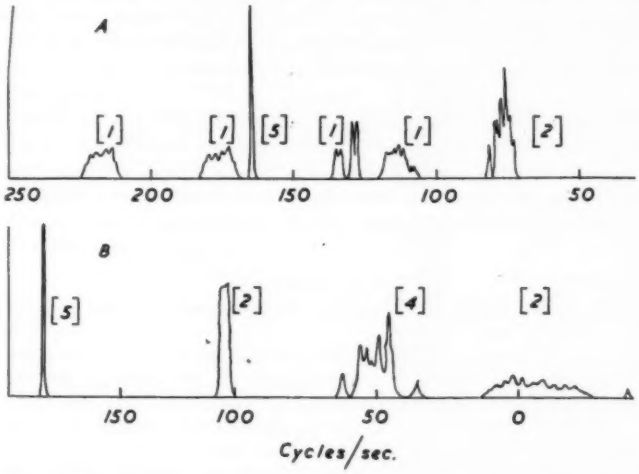
(a) *Nuclear Magnetic Resonance.*—For all compounds containing a hydrogen atom bound to a transition metal this proton is heavily diamagnetically shielded,[1] having a resonance peak in the region 400—800 cycles/sec. (at 40 Mc./sec.) on the high-field side relative to water. Careful measurement of *A* in concentrated solutions in several organic solvents did not give evidence of the presence of such a shielded proton. Structure (I) can thus be eliminated since a band in this region of intensity 0·2 of that of the band due to the protons of the π-*cyclo*pentadienyl ring would have been expected. All proton resonances observed can be accounted for as discussed below. In addition, examination of the sharp peak due to the π-*cyclo*pentadienyl ring protons under very high resolution showed no

[1] Green, Pratt, and Wilkinson, *J.*, 1958, 3916.
[2] Fischer and Wirzmüller, *Z. Naturforsch.*, 1957, **12**b, 737.
[3] Liehr, *Naturwiss.*, 1957, **44**, 61.

evidence of fine structure. In the compound $(\pi\text{-}C_5H_5)_2ReH$ [1] the π-*cyclo*pentadienyl proton line was split into a doublet with peak separation $1{\cdot}0_5$ cycles/sec. due to indirect spin–spin coupling interaction between the proton bound to the metal and those of the ring. The failure to observe such splitting in $C_{10}H_{11}Re(CO)_2$ again indicates the absence of a rhenium–hydrogen bond.

It would also have been expected from (I) that the compound would have a spectrum similar to that of $\pi\text{-}C_5H_5Fe(CO)_2\sigma\text{-}C_5H_5$.[4] A new measurement in carbon disulphide

High-resolution nuclear magnetic resonance spectra of $\pi\text{-}C_5H_5(C_5H_6)Re(CO)_2$ *(A) and* $\pi\text{-}C_5H_5(C_5H_8)Re(CO)_2$ *(B) at 40 Mc./sec. with reference to* cyclo*hexane in cycles/sec. The direction of increasing field is from left to right and the figures in brackets indicate the relative peak areas.*



confirms the previous observation; two peaks are found, one at 134 cycles/sec. (line-width $\leqslant 0{\cdot}7$ cycle/sec.) and one at 188 cycles/sec. (line-width $\simeq 1{\cdot}5$ cycles/sec.), both on the low-field side relative to *cyclo*hexane as zero. The spectrum of the rhenium compound, however, bears no resemblance to that of the iron compound, other than having a sharp π-*cyclo*pentadienyl proton resonance (Figure); there are five other main bands each showing fine structure.

(b) *Infrared Spectra.*—The infrared spectra of compounds containing $\sigma\text{-}C_5H_5$ groups [4] show two peaks at about 3000 cm.$^{-1}$ due to this ring. The spectrum of *A* (Table) shows six peaks in the C–H stretching region in addition to the one at 3112 cm.$^{-1}$ which is assignable to the C–H stretches of the π-*cyclo*pentadienyl ring. The assignment of the other peaks is discussed below.

(c) *Chemical Studies.*—The compound *A* is stable in air and only slowly decomposes in light petroleum; it is stable in carbon tetrachloride even on boiling. It has neither acidic nor basic properties.[2] These properties are quite different from other known metal-complex hydrides (cf. ref. 1).

The unsaturated nature of *A* is shown by rapid decolorisation of bromine in carbon tetrachloride and the formation of an unstable orange precipitate which we have been unable to characterise. On catalytic hydrogenation, however, 1 mol. of hydrogen is absorbed; a white crystalline product, $C_{10}H_{13}Re(CO)_2$, (*B*), was isolated essentially quantitatively. This observation is consistent with structure (II) whereas structure (I) would have required the absorption of 2 mol. of hydrogen. Compound (*B*) must be formulated as π-*cyclo*pentadienyl*cyclo*pentenerhenium carbonyl (III).

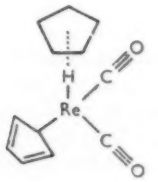
[4] Piper and Wilkinson, *J. Inorg. Nuclear Chem.*, 1956, **3**, 104.

XUM

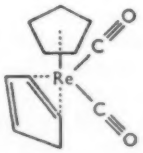
Infrared spectra in carbon disulphide and carbon tetrachloride.

π-$C_5H_5Re(CO)_2C_5H_6$ (cm.$^{-1}$)	π-$C_5H_5Re(CO)_2C_5H_8$ (cm.$^{-1}$)	π-$C_5H_5Re(CO)_2$ (cm.$^{-1}$)	Assignment *
3112 w	**3115 w**	**3117 w**	1
3063 m	—	—	2
3025 m	3020 m	—	3
2954 m	2960 s	—	4
2931 m	2895 m	—	4
2871 s	2855 vs	—	4
2824 m	—	—	
1973 vs	1971 vs	2041 vs	5
1893 vs	1890 vs	1939 vs	5
2480 w	2485 w	2520 w	
2420 w	2425 w	2438 w	
1470 m	—	1820 m	
1450 m	—	—	
1424 m	—	1422 s	
1356 w	1345 m	1349 w	
1292 w	1278 w	—	
1280 m	1257 m	1262 w	
1262 w	—	—	
1220 m	1215 w	—	
1171 vw	1134 s	1190 w	
1127 w	—	—	
1105 s	1103 s	1101 m	
1057 w	1078 s	—	
1040 m	1055 w	1053 w	
1003 m	1003 s	1001 s	
940 m	966 m	—	
914 w	910 w	907 w	
862 m	879 m	—	
—	828 s	—	
810 s	807 s	815 vs	

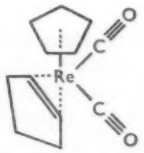
* *Assignments*: 1, C–H stretch of π-C_5H_5; 2, –HC=CH– stretch; 3, –HC=CH– stretch; 4, $>CH_2$ stretch; 5, C≡O stretch.



(I)



(II)



(III)

Discussion

Since the compound $C_{10}H_{11}Re(CO)_2$ has, on the above evidence, neither a σ-*cyclo*pentadienyl ring nor a hydridic proton and contains an olefinic group, it is necessary to assume that one of the double bonds in *cyclo*pentadiene is acting as a donor in a manner similar to that of other olefins in complexes with metals at the end of the transition series.[5] The rhenium atom in this case would then have a closed configuration and the compound would be diamagnetic, as found. The same consideration applies in the case of the hydrogenated compound.

A comparison of the infrared spectra of *A* and *B* in the C–H stretching region indicates that the band at **3063** cm.$^{-1}$ in the former disappears on hydrogenation, whilst the band at **3025** cm.$^{-1}$ is essentially unchanged. The **3063** cm.$^{-1}$ band is hence assigned as the C–H stretch of the unco-ordinated olefinic group in the *cyclo*pentadiene compound. The band at **3025** cm.$^{-1}$ in the *cyclo*pentadiene compound and that at **3020** cm.$^{-1}$ in the *cyclo*pentene compound may be assigned to C–H stretches of the co-ordinated olefin; these are in the same region as the C–H stretches reported in other olefin–metal complexes.[5]

[5] For references see Chatt and Venanzi, *J.*, 1957, 4735.

At present we have too few data on the nuclear magnetic resonance spectra of olefin–metal complexes to allow a detailed analysis of the spectra of compounds *A* and *B*. However, the spectra (Figure) are consistent with the structures (II) and (III). The sharp single peaks at 164—165 cycles/sec. come from the protons in the π-*cyclo*pentadienyl rings. The two bands which occur at *ca.* 175 and ~217 cycles/sec. in the spectrum of *A* are absent from the spectrum of *B*, and can probably be assigned to the protons of the unco-ordinated olefinic group in *A*. The following tentative assignment of the peaks is based on comparisons with the spectra of available measurements on hydrocarbon–metal complexes. In the spectrum of *A*, the lines between 100 and 150 cycles/sec. are assigned to the protons of the co-ordinated olefin group, and the band at 75 cycles/sec. to the methylene group. *cyclo*Pentadiene itself shows two bands, each with much fine structure, at about 185 and 40 cycles/sec. respectively, the latter due to the methylene group. The three bands at 103, 50, and ~0 cycles/sec. in the spectrum of *B* are assigned respectively to the protons of the co-ordinated olefin group, the adjacent ($C_{(3)}$ and $C_{(5)}$) methylene groups, and the $C_{(4)}$ methylene group.

An attempt to prepare *A* directly by refluxing di*cyclo*pentadiene with rhenium carbonyl led to the isolation only of the white crystalline π-*cyclo*pentadienylrhenium tricarbonyl. This compound is very similar in its physical and chemical properties to its manganese analogue.[6] Attempts to substitute one of the carbon monoxide groups in either the manganese or the rhenium compound by *cyclo*pentadiene and *cyclo*hexene in the sealed-tube reactions at 150—200° were unsuccessful.

Experimental

Microanalyses were by the Microanalytical Laboratories, Imperial College. Light petroleum had b. p. 60—80°.

Infrared spectra were measured on a Perkin-Elmer Model 21 spectrometer with both sodium chloride and calcium fluoride optics. High-resolution nuclear magnetic resonance spectra were measured at 40 mc./sec. on a Varian Associates Model 4300B spectrometer with "superstabiliser." The samples were measured at 22° ± 2° c in concentrated solutions in carbon disulphide, contained in spinning 5 mm. o.d. tubes. A loose sealed capillary containing *cyclo*hexane was used as an external reference, and the line positions were measured by the conventional side-band technique.

π-cyclo*Pentadienyl*cyclo*pentadienerhenium Carbonyl.*—Di-π-*cyclo*pentadienylrhenium hydride[1] (1·91 g.) was treated with carbon monoxide at 250 atm. and 100° for three days.[2] The crude brown product was sublimed *in vacuo* at 100°. The pale yellow sublimate was washed with dilute hydrochloric acid to remove unchanged hydride, which was recovered. The remaining solid was crystallised from light petroleum and the product sublimed twice *in vacuo* (1·02 g., 45%), m. p. 111—112° (Found: C, 38·68; H, 3·28; O, 8·25. Calc. for $C_{12}H_{11}O_3Re$: C, 38·58; H, 2·77; O, 8·57%).

π-cyclo*Pentadienyl*cyclo*pentenerhenium Carbonyl.*—An ethyl acetate solution of *A* (19·57 mg. in 25 ml.) with Adams's catalyst absorbed 0·804 ml. of hydrogen, but no more after 12 hr. The solvent was removed and the product crystallised from light petroleum and sublimed, m. p. 95—96° (Found: C, 38·68; H, 3·88. $C_{12}H_{13}O_3Re$ requires C, 38·4; H, 3·90%).

π-cyclo*Pentadienylrhenium Carbonyl.*—Rhenium carbonyl (0·5 g.) was refluxed in 3 ml. of di*cyclo*pentadiene for 4 hr. To the dark brown solution was added 0·5 ml. of light petroleum; on cooling to −70° a pale brown solid was obtained. This was crystallised twice from light petroleum to give white crystals (0·3 g.), m. p. 104—105° (Found: C, 29·0; H, 1·7. $C_8H_5O_3Re$ requires C, 28·7; H, 1·5%). The compound is stable in air and is soluble in common organic solvents; it has a strong camphoraceous odour.

We thank the Department of Scientific and Industrial Research for financial support (M. L. H. G.), Dr. L. Pratt for discussions and assistance with n.m.r. measurements, and Johnson, Matthey and Co. Ltd. for the loan of rhenium.

Inorganic Chemistry Laboratories,
Imperial College of Science and Technology,
London, S.W.7.

[*Received, July 16th,* 1958.]

[6] Piper, Cotton, and Wilkinson, *J. Inorg. Nuclear Chem.*, 1955, **1**, 165.

XUM

877. *Intermediates in Allylic Rearrangements. Part I. The Anionotropy of* 1- *and* 3-*Phenylallyl* p-*Nitrobenzoate.*

By Y. Pocker.

A detailed kinetic investigation of the anionotropic change of 1- to 3-phenylallyl *p*-nitrobenzoate in chlorobenzene at 155·5° is described. The marked difference in ultraviolet light absorption of the two esters made it convenient to follow the isomerisation spectrophotometrically. The rearrangement proceeds to more than 98% completion, is of first order in the ester and is subject to only a mild catalysis by added *p*-nitrobenzoic acid: this catalysis varies linearly with the stoicheiometric proportion of the acid.

Pyridine and *p*-nitrobenzoate salt in concentrations up to 4×10^{-3}M have no effect on the rate of isomerisation, and it is concluded that the isomerisation rate in the absence of any added acid is a purely unimolecular process. The direct proportionality between the acid-catalysed part and the stoicheiometric acid concentration indicates catalysis by monomeric *p*-nitrobenzoic acid molecules.

The general study indicated in the serial title is here begun with two papers on the kinetics of allylic rearrangements in chlorobenzene as solvent. The reaction chosen for investigation is the thermal isomerisation of 1- to 3-phenylallyl esters, which has been extensively investigated [1-4] in various solvents, found to proceed substantially to completion, and to be catalysed by acids. The relative importance of acid-catalysis was far from clear since the rearrangement of 1- to 3-phenylallyl *p*-nitrobenzoate which proceeds in the absence of any externally added acid has been described as being caused entirely,[4a] or at least largely,[4b] by a small amount of *p*-nitrobenzoic acid eliminated from the 1-ester on heating. As these observations were held to invalidate previous conclusions concerning the mechanism by which such isomerisations proceed,[3a,3b] it was important to try to establish unambiguously the existence or otherwise of a neutral isomerisation and its molecularity, as well as the magnitude and the kinetic order of the *p*-nitrobenzoic acid-catalysed reaction. These problems are discussed in the present paper; the nature of the reaction intermediates involved in the isomerisation is considered in Part II.

It is found that surface catalysis is negligible, as rates are practically unaffected by adding crushed glass or packing the reaction tubes with glass wool. The effect of oxygen is also negligible inasmuch as the reaction mixtures sealed in air with exclusion of moisture give practically the same rate as those sealed under dry nitrogen or " oxygen-free " dry nitrogen. The isomerisation rate is also unaffected by the amount of " free " space left above the liquid within the limits tested, *i.e.*, 20—60% of the volume of the reaction tube.

During the isomerisation of 1-phenylallyl *p*-nitrobenzoate in dry chlorobenzene minute quantities of *p*-nitrobenzoic acid are produced. The amount seems to depend on the ester concentration [RX] and on the heating period (see below):

[RX] (mole l.$^{-1}$)	[HX] (mole l.$^{-1}$) Isomerisation (%)		
	25	50	95
0·00312	$>10^{-6}$	—	$\sim 2{\cdot}7 \times 10^{-6}$
0·0312	$2{\cdot}2 \times 10^{-6}$	6×10^{-6}	4×10^{-5}
0·312	2×10^{-5}	5×10^{-5}	3×10^{-4}

However, even when the initial concentration of 1-ester is as high as 0·312M the amount of acid present during most of the isomerisation is too small to have a detectable effect

[1] (*a*) Burton and Ingold, *J.*, 1928, 904; (*b*) Burton, *ibid.*, p. 1650; (*c*) *idem*, *J.*, 1934, 1268.
[2] Meisenheimer, Schmidt, and Schafer, *Annalen*, 1933, **501**, 131.
[3] (*a*) Catchpole and Hughes, *J.*, 1948, 1; (*b*) Catchpole, Hughes, and Ingold, *ibid.*, p. 8.
[4] (*a*) Braude, *Ann. Reports*, 1949, **46**, 125; *Quart. Rev.*, 1950, **4**, 404; (*b*) Braude, Turner, and Waight, *Nature*, 1954, **173**, 863 (Erratum, p. 1075).

XUM

on the rate (see Table 2). Accordingly the isomerisation reaction is not autocatalytic, as can be judged from the constancy in the first-order rate coefficients up to 85% isomerisation (see p. 4323).

The order with respect to 1-phenylallyl *p*-nitrobenzoate is unity. This is illustrated by the constancy in the first-order rate coefficients at various ester concentrations (Table 1). The test here illustrated is for a range of 1 : 1540 of 1-phenylallyl *p*-nitrobenzoate concentrations, and agrees with similar observations by Meisenheimer, Schmidt, and Schafer [2] for solutions in ether and pentane. The present results show that the importance of acid-catalysis has been overestimated; [4a, 4b] for, if *p*-nitrobenzoic acid had indeed been essential for rearrangement, the first-order rate coefficients should have increased both within any one run, and with the initial 1-phenylallyl *p*-nitrobenzoate concentration, the former conclusion arising because longer periods of heating increase the amount of acid produced, and the latter because, acording to the proposed elimination scheme,[4a] the amount of acid eliminated must be proportional to the initial concentration of 1-phenylallyl *p*-nitrobenzoate used.

TABLE 1. *First-order rate coefficients for the rearrangement of* 1-*phenylallyl* p-*nitrobenzoate* (RX) *in chlorobenzene at* 155·5°.

[RX] (M)	$2·02 \times 10^{-4}$	$2·02 \times 10^{-3}$	$2·38 \times 10^{-3}$	$1·17 \times 10^{-2}$
10^5k_1 (sec.$^{-1}$)	1·17	1·15	1·16	1·16
[RX] (M)	$2·38 \times 10^{-2}$	$4·44 \times 10^{-2}$	$1·02 \times 10^{-1}$	$3·12 \times 10^{-1}$
10^5k_1 (sec.$^{-1}$)	1·15	1·15	1·18	1·17

Added p-*Nitrobenzoic Acid.*—By using low concentrations of 1-phenylallyl *p*-nitrobenzoate we can investigate the effect of added *p*-nitrobenzoic acid in concentrations overwhelmingly large relative to the minute traces which may be formed on heating the esters in dry chlorobenzene. For a suitable concentration ($2·02 \times 10^{-4}$M) it can be shown that, even when the ratio of added *p*-nitrobenzoic acid to the initial concentration of 1-phenylallyl *p*-nitrobenzoate is 2·2 : 1, there is practically no increase in the isomerisation rate. In chlorobenzene, saturated at room temperature with *p*-nitrobenzoic acid, the isomerisation rate increases at 155·5° by only about 16%, *i.e.*, from $10^5k_1 = 1·16$ to $10^5k_1 = 1·35$ sec.$^{-1}$ In order to extend the acid-catalysed region further, solubility measurements were carried out in chlorobenzene which indicate that quantities up to about 0·48M in *p*-nitrobenzoic acid can be dissolved at 155·5° In the present investigation, however, quantities were limited to 0·048M-*p*-nitrobenzoic acid since the high rate of dissolution of these lower concentrations (in less than 2 min. in sealed ampoules) ensured a high degree of reproducibility and a completely homogeneous acid-catalysis. Good first-order rate coefficients were obtained throughout any given run (see Table 2). For the presence of

TABLE 2. *First-order rate coefficients of the rearrangement of* 1-*phenylallyl* p-*nitrobenzoate* (RX) *with added* p-*nitrobenzoic acid* (HX) *in chlorobenzene at* 155·5°.

	[RX] = $2·02 \times 10^{-4}$M					[RX] = $2·02 \times 10^{-3}$M			
10^4[HX]	—	0·86	2·15	4·3	—	0·0287	0·718	2·15	4·31
10^5k_1 (sec.$^{-1}$)	1·17	1·14	1·15	1·16	1·15	1·17	1·18	1·18	1·15

[RX] = $4·44 \times 10^{-2}$M

10^3[HX]	—	0·04	0·07	0·21	0·30	0·50	0·96	1·40	2·10	3·30	4·57
10^5k_1 (sec.$^{-1}$)	1·16	1·16	1·20	1·30	1·36	1·49	1·78	2·08	2·53	3·34	4·19

[RX] = $1·024 \times 10^{-1}$M

10^3[HX]	—	0·23	0·43	0·62	0·71	0·86	1·05	1·20
10^5k_1 (sec.$^{-1}$)	1·15	1·32	1·37	1·57	1·63	1·72	1·86	1·95
10^3[HX]	1·38	1·60	1·89	2·46	2·63	3·22	3·56	3·99
10^5k_1 (sec.$^{-1}$)	2·06	2·22	2·42	2·78	2·88	3·28	3·52	3·80

[RX] = $3·12 \times 10^{-1}$M

10^3[HX]	—	0·12	0·15	0·26	0·45	0·60	0·70	1·2
10^5k_1 (sec.$^{-1}$)	1·16	1·24	1·25	1·32	1·46	1·54	1·62	1·94
10^3[HX]	1·37	1·50	1·71	2·08	2·60	3·40	3·80	4·27
10^5k_1 (sec.$^{-1}$)	2·09	2·15	2·29	2·54	2·84	3·40	3·68	4·02

added *p*-nitrobenzoic acid the overall first-order rate coefficient, k_1, can be expressed in the form $k_1 = k_0 + k_{HX}[HX]$, where k_0 is the first-order rate coefficient of the neutral rearrangement, k_{HX} is the catalytic coefficient, and [HX] the stoicheiometric acid concentration.

The values obtained for k_0 and k_{HX} from the different initial concentrations of 1-ester are practically the same, *viz.*, $10^5k_0 = 1{\cdot}16 \pm 0{\cdot}02$ sec.$^{-1}$ and $k_{HX} = 6{\cdot}62 \times 10^{-4}$ l. sec.$^{-1}$ mole^{-1}. It should be noted that the k_0 value obtained on extrapolation to zero acid is practically identical with that independently established by following the isomerisation in the absence of any external added acid.

The linear form of the catalysis shows that the *p*-nitrobenzoic acid molecule is the acting catalyst, catalysis by species arising from dissociated or associated acid molecules being negligible. Electrophilic catalysis by one acid molecule followed by, or synchronous with, an attack by a second acid molecule at the 3-position is also ruled out. The observed linear catalysis is consistent with either an electrophilic catalysis of ionisation by acid molecules, as previously encountered in similar aprotic media,[5b] or with a hydrogen-bonded * S_N2' mechanism, in which one and the same molecule is bonded by hydrogen to the leaving group and attacks the 3-position of the allylic system. The distinction between these alternatives necessitates a comparison between rearrangement and isotopic exchange rates, and is discussed in the following paper (Part II).

Added Pyridine.—The isomerisation rate, as determined in chlorobenzene in the presence of added pyridine, is practically identical with that in the absence of any additive. The pyridine concentration is chosen to be small, yet comparable with the initial ester concentration, and therefore overwhelmingly large compared with the traces of *p*-nitrobenzoic acid formed during the isomerisation. Good first-order coefficients are obtained in any one run, and are independent of the pyridine concentration (see Table 3). In

TABLE 3. *First-order rate coefficients of the rearrangement of* 1-*phenylallyl* p-*nitrobenzoate* (RX) *in the presence of added pyridine* (P) *and tetra*-n-*butylammonium* p-*nitrobenzoate* (Bu^n_4NX) *and chlorobenzene at* 155·5°.

[RX] = 2·02 × 10^{-3}M					[RX] = 2·38 × 10^{-3}M				
10^3[P]	—	1·50	1·82	3·65	10^3[Bu^n_4NX] ...	—	1·51	3·02	4·53
10^5k_1 (sec.$^{-1}$)	1·16	1·15	1·17	1·16	10^5k_1 (sec.$^{-1}$)	1·15	1·15	1·17	1·16

addition to their bearing on the problem of the neutral rate of isomerisation, these results indicate that, within the concentration range used, there is no bimolecular attack by pyridine at the 1- or 3-position of the 1-phenylallyl *p*-nitrobenzoate molecule with subsequent fast decomposition to form 3-phenylallyl *p*-nitrobenzoate and regenerate pyridine. The formation of a pyridinium intermediate following a unimolecular slow ionisation of the 1-ester is not, however, excluded, but limitations are imposed on such a process, for formation of the pyridinium intermediate is governed by the same rate-determining step as the neutral isomerisation, and its breakdown must be fast. Pyridine thus does not provide a by-pass to the rate-determining step of the normal unimolecular isomerisation.

Added Tetra-n-*butylammonium* p-*Nitrobenzoate.*—Catchpole and Hughes [3] have shown that, in methyl cyanide and acetic anhydride, the effect of added lithium *p*-nitrobenzoate, though considerable, is no greater than can be accounted for as an activity effect of an added salt on a reaction whose rate is controlled by an ionic dissociation. The same test is applied in the present investigation but, since alkali and lower tetra-alkylammonium-*p*-nitrobenzoates are practically insoluble in chlorobenzene, tetra-*n*-butylammonium *p*-nitrobenzoate had to be employed. Unfortunately, at the high temperature used for

* A hydrogen-bonded S_N2' rather than a simple S_N2' mechanism must be suggested because stronger nucleophilic agents (Bu^n_3N, C_5H_5N, and *p*-$NO_2{\cdot}C_6H_4{\cdot}CO_2NBu^n_4$) have practically no effect on the isomerisation rate.

[5] (*a*) Hughes, Ingold, Patai, and Pocker, *J.*, 1957, 1206; (*b*) Hughes, Ingold, Mok, and Pocker, *ibid.*, p. 1238.

XUM

the isomerisation, ~30% decomposition sets in to produce tri-*n*-butylamine and *n*-butyl *p*-nitrobenzoate. Since, however, the rearrangement rate is practically unaffected by the added salt, one has to conclude that neither tetra-*n*-butylammonium *p*-nitrobenzoate ion-pairs nor tri-*n*-butylamine, at the concentrations used, attacks the 3-position with consequent rearrangement. Mechanism S_N2' is thus not operative under the conditions used, because one cannot by-pass the rate-determining step of the normal unimolecular isomerisation.

Experimental

Materials.—Chlorobenzene (B.D.H.), unless otherwise indicated, was dried ($CaCl_2$) for long periods, and fractionated in an all-glass, helix-packed column of about 20 theoretical plates, head and tail fractions being rejected; the middle fraction, b. p. 131·5—132°, was used. Chlorobenzene, fractionated as above, after treatment with phosphoric oxide or anhydrous potassium carbonate, gave practically the same isomerisation rates:

Drying agent	$CaCl_2$	P_2O_5	K_2CO_3
10^5k_1 (sec.$^{-1}$)	1·15	1·16	1·15

Chlorobenzene, purified as above and heated for two weeks at 155·5°, shows no change in its ultraviolet absorption spectrum, and tests for traces of hydrogen chloride are negative. An isomerisation run performed in this chlorobenzene at 155·5° gave $10^5k_1 = 1·15$ sec.$^{-1}$.

Pyridine (B.D.H.) was dried by the method of Burgess and Kraus [6] and subjected to the same fractionation as above. The middle fraction, b. p. 115·5°, was used. Pyridine was also dried over, and twice fractionated from, freshly fused potassium hydroxide, with exclusion of moisture. First-order rate coefficients of the rearrangements of 1-phenylallyl *p*-nitrobenzoate ($2·02 \times 10^{-3}$) in the presence of pyridine ($1·5 \times 10^{-3}$M) purified by either method gave:

Purification method	Burgess and Kraus	Fused KOH
10^5k_1 (sec.$^{-1}$)	1·16	1·16

Commercial methyl alcohol was purified by Bjerrum and Zechmeister's method,[7] and had n_D^{25} 1·3271 (lit.,[8] 1·3271).

Commercial ethyl alcohol was dried by Lund and Bjerrum's method [9] and fractionated with exclusion of moisture under oxygen-free nitrogen. This product was superior for measurements in the ultraviolet region to the one purified, with similar precautions, by Smith's or Manske's procedure.[10a,b]

1-Phenylallyl alcohol was prepared by reaction of phenylmagnesium bromide [from magnesium (24 g.) in ether (600 ml.)] with an ethereal solution (300 ml.) of freshly distilled acraldehyde (56 g.) during 1 hr. at about −10° and then for 3 hr. at −5°, in dry oxygen-free nitrogen. The mixture was decomposed with cold saturated aqueous ammonium chloride. The combined extracts were dried (K_2CO_3) and distilled from a trace of this carbonate. The middle fraction, b. p. 52°/0·2 mm., n_D^{25} 1·5393, was used. The head fraction contained some diphenyl (a side product from the decomposition of phenylmagnesium bromide), and the tail fraction traces of cinnamyl alcohol. The light absorption of the middle fraction (in absolute ethanol) had max. at 2525 and 2580 Å (ε 285 and 280, respectively).

3-Phenylallyl alcohol (B.D.H.) was fractionated (b. p. 130°/15 mm.) and the middle fraction used (m. p. 36°).

1-*Phenylallyl* p-*Nitrobenzoate.*—1-Phenylallyl alcohol (10 g.) in dry pyridine (10 ml.) was added to a mixture of freshly distilled *p*-nitrobenzoyl chloride (11·1 g.) in dry pyridine (20 ml.) at −10°. After 2 days at room temperature, the mixture was poured into aqueous sodium hydrogen carbonate. The ethereal extracts were washed with bicarbonate solution, then water, and crystallised alternately from absolute methyl alcohol and light petroleum (b. p. 60—80°); the product had m. p. 46° (Burton and Ingold [1a] give 45—46°; Meisenheimer, Schmidt, and Schafer [2] give 46·2°); a light absorption max. (in absolute ethanol) was at 2585 Å (ε 14,000).

[6] Burgess and Kraus, *J. Amer. Chem. Soc.*, 1948, **70**, 706.
[7] Bjerrum and Zechmeister, *Ber.*, 1923, **56**, 894.
[8] Hughes and Vernon, *J. Phys. Colloid Chem.*, 1952, **56**, 927.
[9] Lund and Bjerrum, *Ber.*, 1931, **64**, 211.
[10] (*a*) Smith, *J.*, 1927, 1288; (*b*) Manske, *J. Amer. Chem. Soc.*, 1931, **53**, 1106.

3-Phenylallyl *p*-nitrobenzoate, prepared in a similar manner, and recrystallised alternately from ethyl alcohol and light petroleum (b. p. 60—80°), had m. p. 76·5° (Hill and Nason [11] give 78°; Burton and Ingold [1] give 77—78°; Meisenheimer, Schmidt, and Schafer [2] give 76·5°); in absolute ethyl alcohol it had $\lambda_{max.}$ 2550 Å (ε 30,500).

p-*Nitrobenzoic Acid.*—The B.D.H. product was crystallised twice from water and twice from benzene and dried (over P_2O_5) under a good vacuum.

Tetra-*n*-butylammonium *p*-nitrobenzoate was prepared by exact neutralisation of the hydroxide with the acid. After evaporation to dryness the product was dried for one week over P_2O_5 under reduced pressure, and recrystallised from dry benzene. The pale yellow crystals were dried for 5 days under $\sim 10^{-5}$ mm., a liquid-air finger trap being kept above the crystals.

Spectrophotometry.—The marked difference in ultraviolet light absorption of 1- and 3-phenylallyl *p*-nitrobenzoates makes it convenient to follow the isomerisation spectrophotometrically. The measurements were carried out in a Unicam Quartz Spectrophotometer Model S.P. 500. The 656·3 mμ line from the hydrogen lamp was used for calibration, and the photometric accuracy of the instrument was checked with potassium hydrogen phthalate solutions: it fell within the range reported by Ewing and Parsons.[12] The optical density was measured in absolute ethanol in which the two esters, with and without *p*-nitrobenzoic acid, were shown to behave as independently absorbing substances. The rearrangement in carefully purified chlorobenzene is almost free from side reactions as indicated by a >98% conversion into the thermodynamically stable isomer.

The extinction coefficient, when 1-phenylallyl *p*-nitrobenzoate is left to rearrange in chlorobenzene for 10 half-life times, is 98% of the corresponding value for pure 3-ester; when left for 20 half-life times it is only 96% of the theoretical value. Pure 3-phenylallyl *p*-nitrobenzoate on similar treatment shows a reduction of 2% and 4% respectively in its extinction coefficient, which is largely due to the polymerisation of the styryl system. The isomerisation itself seems, therefore, to be practically complete, and for this reason the extinction coefficient of pure 3-phenylallyl *p*-nitrobenzoate was used as " infinity " in calculating rate coefficients.

Kinetic Measurements.—The thermostat was kept at 155·5° ± 0·02°. All-glass apparatus was baked for a long time at 160° before work with chlorobenzene solutions. Known amounts of 1-phenylallyl *p*-nitrobenzoate, either alone or with reagent, were dissolved in chlorobenzene at room temperature, and aliquot parts enclosed in ampoules and heated in the thermostat for various times. After the heating, known amounts of the mixture were pipetted into a series of bulbs specially constructed for vacuum-work. The bulbs were connected through a series of traps to a vacuum-system, and the solvent was removed at room temperature. The residue was dissolved in pure absolute ethanol, and the optical density recorded in the range 240—260 mμ. Point-by-point extinction measurements were made at 0·5 mμ intervals. The dilution was adjusted so as to bring the value of the optical density at 255 mμ into the most accurate range of the spectrophotometer. When quantities of *p*-nitrobenzoic acid in excess of their solubility at room temperature were used, the acid was weighed directly into each ampoule, aliquot parts of 1-ester in chlorobenzene were added, and the sealed ampoules heated for various periods. On cooling, the acid which crystallised was separated, and from known aliquot portions of the filtrate the solvent was removed as described above. The amount of rearrangement was then evaluated after subtraction of the corresponding optical density of the *p*-nitrobenzoic acid present. The acid was determined for each point in the run. This actually provided a double check, since the amount of acid left in solution on cooling to room temperature was practically constant. Independent tests have shown that the esters present in solution were not absorbed by the crystallising acid.

In runs in which tetra-*n*-butylammonium *p*-nitrobenzoate was employed the amount of rearrangement was calculated after correction of the change in optical density for the independently determined increase which accompanies the partial decomposition:

$$p\text{-}NO_2\cdot C_6H_4\cdot CO_2NBu^n_4 \rightleftharpoons Bu^n_3N + p\text{-}NO_2\cdot C_6H_4\cdot CO_2Bu^n$$

The first-order rate coefficients (k_1 in sec.$^{-1}$) were calculated from the formula

$$k_1 = (2{\cdot}303/t)\log_{10}(D_\infty - D_0)/(D_\infty - D_t)$$

[11] Hill and Nason, *J. Amer. Chem. Soc.*, 1924, **76**, 2236.
[12] Ewing and Parsons, *Analyt. Chem.*, 1948, **20** 423.

XUM

where D_0, D_t, and D_∞ are the optical densities at 255 mμ and refer to readings at kinetic zero, time t, and pure 3-phenylallyl *p*-nitrobenzoate respectively, all at the same dilution. A sample run is given below.

[1-Phenylallyl *p*-nitrobenzoate] = $1{\cdot}01 \times 10^{-3}$M

t (min.)	0	150	300	450	600	750	900	1200	1500	1800	3000	4000
D (255 mμ)	0·276	0·310	0·338	0·366	0·390	0·413	0·429	0·466	0·493	0·514	0·570	0·589
Rearrangement (%)	0	10·19	18·55	26·95	35·2	71·0	45·8	56·8	65·0	85·2	88	93·6
$10^5 k_1$ (sec.$^{-1}$)	—	1·17	1·14	1·16	1·16	1·17	1·13	1·17	1·16	1·15	1·18	1·15

k_1 (mean) = $1{\cdot}16 \times 10^{-5}$ sec.$^{-1}$.

After 8 days at 155·5°: D (255 mμ) = 0·603 (*i.e.*, 98% of theoretical infinity)
,, 16 ,, ,, D (255 mμ) = 0·598 (*i.e.*, 96% ,, ,,)
Theoretical infinity: D (255 mμ) = 0·610

The author is indebted to Professor E. D. Hughes, F.R.S., for drawing his attention to this problem, to him and to Sir Christopher Ingold, F.R.S., for helpful discussions, and to the Humanitarian Trust and the Friends of the Hebrew University for a Fellowship during 1951.

William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1. [*Received, May 30th*, 1958.]

---

878. *Intermediates in Allylic Rearrangements. Part II.*[1] *Rates and Mechanism of Exchange and Rearrangement in* 1- *and* 3-*Phenylallyl Benzoate.*

By Y. Pocker.

The isomerisation of 1- to 3-phenylallyl benzoate in chlorobenzene is of first order in ester, is unaffected by added pyridine, and shows linear catalysis with added benzoic acid. The overall rates of loss of ^{18}O from labelled benzoic acid or saline benzoate during the rearrangement of the 1-ester approximate to the isomerisation rates, while under similar conditions the rates of isotopic exchange with the 3-ester are negligible. The loss of tracer from benzoic acid is accounted for by exchange taking place during the rearrangement of the 1-ester and leading to isotopic enrichment into the 1- and the 3-position, *i.e.*, with and without rearrangement.

The rate of production of ^{18}O-labelled 3-ester from normal 1-ester and labelled saline benzoate is only 70—75% of the isomerisation rate, so that about 25—30% of the isomerisation proceeds with no isotopic exchange. The rate at which tracer is introduced into the 1-ester is about 15—20% of the isomerisation rate. An explanation in terms of ion-pair intermediates is proposed.

The isomerisation of 1- to 3-phenylallyl *p*-nitrobenzoate, in the absence of added acid, in chlorobenzene, is a unimolecular process (see Part I) which may in principle be inter- or intra-molecular. The present investigation attempts to distinguish between these alternatives with the help of ^{18}O isotopic tracer experiments. The corresponding allylic benzoates were used because partial separation from a mixture containing the two isomers and subsequent pyrolysis proved to be experimentally easier. An additional advantage is that the problem of a possible dilution of ^{18}O derived from the carboxylic group by the normal oxygen atoms of the nitro-group, during the high-temperature pyrolysis which precedes the mass-spectrometric analysis, does not arise.

As for *p*-nitrobenzoates,[1] the marked difference in ultraviolet light absorption of 1- and 3-phenylallyl benzoate made it convenient to follow the rearrangement spectrophotometrically. Measurements carried out on synthetic mixtures in absolute ethyl alcohol show that the compounds behave as independently absorbing mixtures. Optical-density

[1] Part I, preceding paper.

XUM

measurements were carried out in the region 240—255 mμ, and the values at 250 mμ were used for calculating first-order rate coefficients. In some cases these were checked against values calculated from measurements at other convenient wavelengths, and the agreement was good. The rearrangement of 1- to 3-phenylallyl benzoate in dry chlorobenzene at 155·5° gives good first-order rate coefficients which are practically identical for a variation of 1 : 1000 in the initial 1-ester concentration (see Table 1).

TABLE 1. *First-order rate coefficients* k_1 *(in sec.*$^{-1}$*) for the rearrangement of* 1*-phenylallyl benzoate* ($Ph{\cdot}CO_2R$) *in chlorobenzene at* 155·5°*, with and without added pyridine* (P).

10^3[$Ph{\cdot}CO_2R$]	0·35	3·5	35	350
10^6k_1	0·99	1·02	0·99	1·00

A partly isomerised sample containing initially 15·6% of 3-phenylallyl benzoate gives $10^6k_1 = 0{\cdot}99$ sec.$^{-1}$.

[$Ph{\cdot}CO_2R$] = 0·035M

[P]	0·02	0·045	0·103
10^6k_1	1·00	1·00	1·08

The amount of benzoic acid produced under kinetic conditions during the first 20% of reaction was too small to be detected. The rate of neutral rearrangement of 1-phenylallyl benzoate in chlorobenzene at 155·5° is 11·6 times less than the rate for the corresponding *p*-nitrobenzoate. This result accords with what would be expected on the basis of Burton and Ingold's theory,[2] *i.e.*, that the ease of rearrangement increases in the order of stability of the anion. This order is indicated, in turn, by the strength of the corresponding acids.

Added Pyridine.—Pyridine in concentration up to 0·045M (Table 1) had no observable effect on the isomerisation rate. This concentration was 1·3 times larger than that of 1-isomer originally introduced, and therefore overwhelmingly larger than the traces of acid which might be formed during the isomerisation. These observations support the value given in the previous section for the rate of neutral isomerisation. The relatively negligible increase in rate observed with 0·103M-pyridine shows that a bimolecular attack with rearrangement, an S_N2' reaction, does not take place to any kinetically significant extent at these concentrations.

Added Benzoic Acid.—The addition of benzoic acid catalyses the rearrangement (see Table 2). The catalysis is linear with respect to stoicheiometric acid concentration. The overall first-order rate coefficient, k_1^R, can be expressed by the equation: $k_1^R = k_0^R + k^R_{Ph{\cdot}CO_2H}[Ph{\cdot}CO_2H]$, where k_0^R is the first-order rate coefficient for neutral rearrangement ($10^6k_0^R = 0{\cdot}99$ sec.$^{-1}$ at 155·5°), and $k^R_{Ph{\cdot}CO_2H}$ is the catalytic coefficient for benzoic acid ($10^6k^R_{Ph{\cdot}CO_2H} = 34{\cdot}4$ l. mole^{-1} sec.$^{-1}$ at 155·5°).

Exchange with ^{18}O*-Benzoic Acid.*—When 1-phenylallyl benzoate is heated in the presence of ^{18}O-benzoic acid in chlorobenzene at 155·5°, the acid recovered at various intervals shows a steady diminution of its ^{18}O content. The amount of acid was shown to remain constant throughout the various heating periods, thereby excluding any decomposition of the ester to 1-phenylallene and benzoic acid[3] of natural isotopic abundance. The ^{18}O content found in the mixture of isomers corresponds practically quantitatively to the isotopic dilution found in the acid, proving that isotopic exchange takes place. On the other hand, when the rearranged isomer, the 3-phenylallyl benzoate, is heated with ^{18}O-labelled benzoic acid for periods up to 120 hr. at 155·5° there is practically no isotopic dilution of the acid [*e.g.*, heating 0·198M-3-phenylallyl benzoate with ^{18}O-enriched 0·224M-benzoic acid for 0, 72, 96, and 120 hr. gave values of β′ (^{18}O atoms % excess above normal) = 1·69, 1·70, 1·68, and 1·68, respectively]. The observed exchange with 1-phenylallyl benzoate must therefore take place either before or during rearrangement. The rates of isotopic equilibration between enriched benzoic acid and 1-phenylallyl benzoate of normal abundance were determined for a given ester concentration and varying acid concentration

[2] Burton and Ingold, *J.*, 1928, 904.
[3] Braude, *Ann. Reports*, 1949, **46**, 125; *Quart. Reviews*, 1950, **4**, 404.

XUM

in chlorobenzene at 155·5°. Under these conditions the rearranged isomer can undergo only a negligible amount of isotopic exchange after formation. First-order rate coefficients for exchange, k_1^E, are therefore calculated with respect to 1-phenylallyl benzoate left after various periods of heating. The results are given in Table 2.

TABLE 2. *First-order rate coefficients of rearrangement* (k_1^R *in sec.*$^{-1}$) *and exchange* (k_1^E *in sec.*$^{-1}$) *for the reaction of* 1-*phenylallyl benzoate* (1-Ph·CO_2R) *with varying amounts of benzoic acid in chlorobenzene at* 155·5°.

[1-Ph·CO_2R] = 3·50 × 10^{-3}M

10^3[Ph·CO_2H]	0·00	0·90	1·80	2·90	4·42	5·00	6·20	6·63	7·00	7·48
$10^5k_1^E$	0·99	1·30	1·60	1·99	2·52	2·70	3·12	3·30	3·49	3·56
10^3[Ph·CO_2H]	1·99	4·42	6·20	7·48						
$10^6k_1^E$	1·5	2·3	2·7	3·1						

The first-order rate coefficient for overall exchange, k_1^E, can be expressed by the linear equation:

$$k_1^E = k_0^E + k^E_{Ph\cdot CO_2H}[Ph\cdot CO_2H]$$

where the first-order rate coefficient for neutral exchange, k_0^E, is about 0·9 × 10^{-6} sec.$^{-1}$ and the catalytic coefficient for exchange with benzoic acid, $k^E_{Ph\cdot CO_2H}$, is about 0·29 × 10^{-4} l. mole^{-1} sec.$^{-1}$. The ratio of exchange to rearrangement rates under neutral conditions, k_0^E/k_0^R, is approximately 0·90, and the ratio of the corresponding catalytic coefficients, $k^E_{Ph\cdot CO_2H}/k^R_{Ph\cdot CO_2H}$, is approximately 0·85.

*Added Tetra-*n*-butylammonium* [^{18}O]*Benzoate.*—The importance of an S_N2' mechanism under non-acidic conditions was tested by studying the effect of a benzoate salt (tetra-*n*-butylammonium [^{18}O]benzoate) on the rates of isomerisation and exchange of 1-phenylallyl benzoate. At the high temperature used (155·5°) a relatively mobile equilibrium is set up between the salt and its decomposition products, *n*-butyl benzoate and tri-*n*-butylamine, so that any isotopic exchange between enriched benzoate salt ion-pairs and 1-phenylallyl benzoate of normal abundance is almost immediately equilibrated with *n*-butyl benzoate. Exchange rates were therefore evaluated on the assumption that all the ^{18}O initially present in the benzoate salt is readily available for isotopic equilibration.

The first-order rate coefficient for the isomerisation of 0·248M-1-phenylallyl benzoate in the presence of originally introduced 0·0887M-Ph·$CO_2NBu^n_4$ in chlorobenzene at 155·5° is 1·25 × 10^{-6} sec.$^{-1}$, the corresponding rate of exchange being 1·16 × 10^{-6} sec.$^{-1}$. Increases of about 25% in the corresponding rates of rearrangement and exchange in the presence of a relatively high salt concentration are compatible with ion-pair catalysis on a reaction whose transition state is more polar than its initial state. Any attempt by benzoate ion-pairs or tri-*n* butylamine to by-pass the rate-determining step of the unimolecular isomerisation (*e.g., via* an S_N2' process) must be relatively small. The ratio of rate of exchange to that of rearrangement in the presence of benzoate salt ion-pairs (and possibly very minor Bu^n_3N catalysis) is 0·94, in good agreement with 0·9, the value obtained for the neutral region by extrapolation (previous section).

Isotopic Product Analysis.—1-Phenylallyl benzoate (0·0340M) of normal abundance and ^{18}O-enriched benzoic acid (0·062M) or tetra-*n*-butylammonium benzoate (0·0977M) were heated in chlorobenzene at 155·5° to 50% rearrangement. The mixture of isomers was partly separated into fractions rich in 1- and 3-phenylallyl benzoate. A portion of each fraction was quantitatively pyrolysed to benzoic acid, and the carbon dioxide obtained from the decomposition of the corresponding silver salts was mass-spectrometrically analysed. With both acid and benzoate salt the 1-isomer was found to contain about one-fifth * of the ^{18}O atoms excess above normal lost by the acid or salt, while the 3-isomer contained the remaining four-fifths. Account being taken of the ratio of the rate

* This result is qualitatively similar to that obtained by Meisenheimer and Beutter (*Annalen*, 1934, **508**, 58) who found that 3-phenylallyl chloride in acetic acid produces a mixture of acetates containing 18% of the 1-phenylallyl compound.

of total exchange to rate of rearrangement, this means that about 70—75% of the rearrangement proceeds with isotopic exchange and about 25—30% must proceed intramolecularly.

Discussion of Mechanism.—(1) Isotopic exchange between acid (HX*) and ester (RX) *before* rearrangement followed by intramolecular isomerisation: [5]

$$RX + HX^* \rightleftharpoons RX^* + HX$$
$$RX^* \xrightarrow{S_Ni} R'X^*$$

is largely excluded by observations (*a*) and (*b*): (*a*) The total rate of exchange contains a relatively large zero-order component in benzoic acid (*e.g.*, $k_0^E = 0{\cdot}9k_0^R$), whereas this mechanism demands $k_0^E = 0$. (*b*) The amount of enrichment in the 3-isomer is larger than that found in the unrearranged material. Also, contrary to the present results, the expected order of reactivity for S_N2 reactions is primary > secondary.

(2) Isotopic exchange *after* rearrangement,[5] *viz.*,

$$RX \xrightarrow{S_Ni} R'X$$
$$R'X + HX^* \rightleftharpoons R'X^* + HX$$

is excluded by the observation that the exchange between the 3-isomer and benzoic acid is negligible under conditions where the 1-isomer undergoes both exchange and rearrangement.

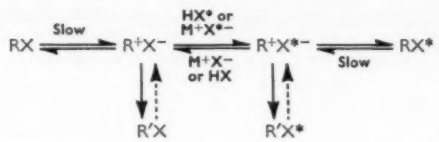
(3) A one-stage bimolecular mechanism with rearrangement (S_N2') cannot be responsible for the total rate of exchange, because under the experimental conditions it must be of second-order, *i.e.*, of first order in each component, while the experiments show that a considerable part of both exchange and rearrangement is of zero order with respect to either benzoic acid or benzoate salt; *i.e.*, neither k_0^R nor k_0^E is zero. The catalytic coefficient for rearrangement is larger than that for exchange in the 3-position, and so even the acid-catalysed part cannot be entirely an S_N2' reaction.

(4) The results are in agreement with the occurrence of an isotopic exchange in the 1- and the 3-position during the rearrangement. The simplest interpretation of the neutral component of exchange is in terms of an ionisation mechanism (S_N1), as modified in a solvent of low ionising power, to contain a rate-determining ionisation to phenylallyl carbonium benzoate ion-pairs.[6,7] The original ion of the ion-pair has a greater chance than a chemically equivalent external anion to recombine with the carbonium cation, thereby leading to a rearrangement faster than exchange into the 3-position. This result and steric considerations of the ion-pairs involved [7] explain why in the absence of added reagents the acyl oxygen of the starting material may largely become [8] the alkyl oxygen in the rearranged product.*

* On the simple ionisation theory, if 30% of the isomerisation proceeds intramolecularly then in the absence of added reagents, 65% (*i.e.*, $30 + \frac{1}{2} \times 70\%$) of the acyl-oxygen atoms in the starting material may be expected to become alkyl-oxygen atoms in the rearranged product. However, even if the latter percentage came out to be higher, this would not preclude the exchange from showing zero-order dependence on substituting agent. Such a dependence only shows that the transition state for the neutral exchange is formed as easily in one concentration of added reagent as in another, and any particularisation of this conclusion as to the degree of ion separation is not necessitated by the present exchange results. Thus a low degree of " scrambling " of carbonyl and alkoxyl oxygen atoms in the absence of added reagent and a zero-order dependence on substituting reagent are two complementary results which would be consistent with the modified picture for S_N1 substitutions in benzene.[9]

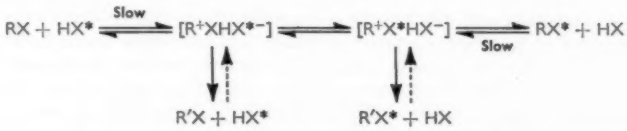
[4] Catchpole and Hughes, *J.*, 1948, 1.
[5] Braude, Turner, and Waight, *Nature*, 1954, **173**, 863 (Erratum, p. 1075).
[6] Hughes, Ingold, Mok, Patai, and Pocker, *J.*, 1957, 1220, 1265.
[7] (*a*) Winstein and Robinson, *J. Amer. Chem. Soc.*, 1958, **119**, 169; (*b*) Winstein's contribution to Discussion " Symposium on Molecular Rearrangements," Queen Mary College, Univ. London, April 6th, 1954; *Nature*, 1954, **173**, 898; *Chem. Eng. News*, 1954, **32**, 1898.
[8] (*a*) Braude and Turner, *Chem. and Ind.*, 1955, 1223; (*b*) Doering, quoted by Goering and Greiner, *J. Amer. Chem. Soc.*, 1957, **79**, 3467.
[9] Hughes, Ingold, Mok, Patai, and Pocker, *J.*, 1957, 1265.

XUM



The transition state for ion-pair collapse with rearrangement is only somewhat lower in energy than the corresponding transition state for ion-pair return with exchange, and bears no relation to the large energy of conjugation of a phenyl with a vinyl system which affects only the position of equilibrium.

The acid-catalysed component can be explained in terms of an electrophilic cataly is of the slow ionisation process:



That the acid-catalysed component is mechanistically similar to the neutral rearrangement is supported by the observation that the ratios k^E/k^R and $k^E_{Ph\cdot CO_2H}/k^R_{Ph\cdot CO_2H}$ are not very different, so that the electrophilic catalysis of ionisation does not affect the possible fates of the carbonium benzoate ion-pairs.

Experimental

Materials.—The purification of chlorobenzene, pyridine, and ethyl alcohol is described in the preceding paper.

1-Phenylallyl benzoate was prepared by adding to a cooled mixture of 1-phenylallyl alcohol (55 g.) and pyridine (30 ml.), freshly distilled benzoyl chloride (57 g.) in pyridine (60 ml.) during 1 hr. After 2 days at room temperature, the mixture was worked up as for the corresponding *p*-nitrobenzoate; the product had b. p. 90°/10^{-5} mm., n_D^{26} 1·5630. Isotopic dilution experiments indicated complete absence of free benzoic acid. Light absorption max. in absolute ethyl alcohol in the region 240—280 mμ were at 263 and 271·5 mμ (ε 1070 and 1030, respectively). Rupe and Miller [10] give b. p. 182°/12 mm.; a sample distilled at this high temperature was found to contain 15·6% of the corresponding 3-isomer, n_D^{25} 1·5669. 3-Phenylallyl benzoate was prepared as above except that the reaction mixture was left at room temperature for 3 days; the product had b. p. 110°/10 mm., m. p. 35° (from light petroleum), $\lambda_{max.}$ in absolute ethanol 250 mμ (ε 21,900).

[^{18}O]Benzoic acid was prepared by prolonged heating of benzoic acid of normal abundance with water samples containing 1·5—2·2% of ^{18}O excess above normal.[11]

Tetra-*n*-butylammonium [^{18}O]benzoate was prepared by exact neutralisation of the hydroxide with [^{18}O]benzoic acid. The dry product was kept for 2 weeks over P_2O_5 under a good vacuum, recrystallised from dry benzene–light petroleum, and dried for one week at 10^{-7} mm. (Found: C, 75·4; H, 11·3; N, 3·85. Calc. for $C_{23}H_{41}O_2N$: C, 76·0; H, 11·4; N, 3·8%).

Kinetic Methods.—All-glass apparatus was baked for a long time at 160° before work with chlorobenzene solutions. The reaction mixtures were heated in sealed ampoules at 155·5° for various periods and worked up as described in the preceding paper.

Spectrophotometric Measurements.—These were carried out in the region 240—260 mμ, and the rates calculated from readings at 250 mμ.

The first-order rate coefficients, k_1 (in sec.$^{-1}$), were calculated from the formula:

$$k_1 = (2{\cdot}303/t) \log_{10} (D_\infty - D_0)/(D_\infty - D_t)$$

where D_0, D_t, and D_∞ are optical densities at 250 mμ and refer to readings at zero time, time t,

[10] Rupe and Miller, *Helv. Chim. Acta*, 1921, **4**, 841.
[11] Roberts and Urey, *J. Amer. Chem. Soc.*, 1939, **61**, 2580.

XUM

and pure 3-phenylallyl benzoate respectively, all at the same dilution. Sample runs are given below:

[1-Phenylallyl benzoate] = 0·035M; D_∞ (theor.) = 2·400.

t (min.)	0	1200	1500	2200	3000	3600	4800	6000	6600	8000	10,000
D	0·220	0·376	0·404	0·494	0·577	0·630	0·771	0·875	0·918	1·04	1·20
10^6k_1 (sec.$^{-1}$)	—	1·02	0·98	1·01	0·99	0·96	1·01	0·99	0·97	0·98	0·995

[1-Phenylallyl benzoate] = 0·035M; [Pyridine] = 0·045M; D_∞ (theor.) = 1·450.

t (min.)	0	1500	3960	4500	6000	8000	9000	11,400	13,020
D	0·133	0·430	0·580	0·600	0·669	0·778	0·798	0·888	0·934
10^6k (sec.$^{-1}$)	—	0·955	1·03	0·995	0·982	1·045	0·985	1·00	0·983

Isotopic Measurements.—(a) *Analysis of* ^{18}O *content of benzoic acid.* Samples isolated at various times were pumped off, leaving a mixture of 1- and 3-phenylallyl benzoate and benzoic acid. The acid was extracted with insufficient alkali hydroxide (to ensure that no hydrolysis takes place). (Extraction with alkali hydrogen carbonate and then working up of the solution at pH 5—6 resulted in dilution of tracer, probably because of the difficulty of removing the last traces of carbon dioxide at this pH.) Silver benzoate was precipitated from sodium benzoate at pH ~5—6, washed with water, alcohol, and ether, dried at 110—120°, and kept in a vacuum-desiccator. Samples (10—30 mg.) were decarboxylated by heat *in vacuo*; the carbon dioxide entered the mass spectrometer through a trap at −80°. The isotopic abundance of the oxygen was measured by comparing masses 44 and 46 corresponding to $^{12}C^{16}O^{16}O$ and $^{12}C^{16}O^{18}O$. The contribution to mass 46 from $^{13}C^{16}O^{17}O$ was neglected. If R is the ratio of the peaks 44 and 46, the abundance in atoms % of ^{18}O is given by $\beta = 100/(2R + 1)$. The values quoted, β', are excess above normal in carbon dioxide. These measurements were carried out in a 180° mass spectrometer of 10 cm. radius of curvature and a single collector with voltage scanning.

Calculation of isotopic results. The change in the concentration of labelled benzoic acid [HX*] with time equals the total concentration of benzoic acid [HX] multiplied by the change in excess abundance with time:

$$-\mathrm{d[HX^*]}/\mathrm{d}t = -[\mathrm{HX}]\ \mathrm{d}\beta'/\mathrm{d}t$$

Since the 3-isomer, once formed, undergoes only a negligible amount of exchange (see first example below) the change in concentration of labelled benzoic acid with time is proportional to the concentration of the 1-isomer left at time t and to the excess abundance at time t of the labelled benzoic acid:

$$-\mathrm{d[HX^*]}/\mathrm{d}t = k_1^{\mathrm{E}}\ [\mathrm{RX}]_t\ \beta'_t$$

This leads to $-[\mathrm{HX}]\ \mathrm{d}\beta'/\mathrm{d}t = k_1^{\mathrm{E}}\ [\mathrm{RX}]_t\ \beta'_t$, where $[\mathrm{RX}]_t = [\mathrm{RX}]_0 \exp(-k_1^{\mathrm{R}}t)$, so that

$$-\int_0^t \mathrm{d}\beta'/\beta' = k_1^{\mathrm{E}}\frac{[\mathrm{RX}]_0}{[\mathrm{HX}]}\int_0^t \exp(-k_1^{\mathrm{R}}t)$$

or

$$2{\cdot}303\ \log_{10}(\beta_0'/\beta'_t) = k_1^{\mathrm{E}}\frac{[\mathrm{RX}]_0}{[\mathrm{HX}]}\ \frac{1-\exp(-k_1^{\mathrm{R}}t)}{k_1^{\mathrm{R}}}$$

For calculating the isotopic results the above formula was used.

Examples:

[3-Phenylallyl benzoate] = 0·198M; [^{18}O]benzoic acid = 0·224M. Temp. 155·5°; chlorobenzene solution.

t (hr.)	0	72	96	120
β'	1·69	1·70	1·68	1·68

[1-Phenylallyl benzoate] = 0·035M; β'_0 (benzoic acid) = 1·92.

10^3[Ph·CO_2H]	1·99	4·42	6·20	7·48
t (min.)	1680	1500	1200	1200
β'_t	1·486	1·654	1·733	1·75
$1-\exp(-k^{\mathrm{R}}t)$	0·154	0·201	0·200	0·226
$10^6k_1^{\mathrm{E}}$ (sec.$^{-1}$)	1·5	2·3	2·7	3·1

XUM

(b) *Analysis of* ^{18}O *content of the isomeric esters.* 1- and 3-Phenylallyl benzoate were converted into carbon dioxide in two steps. The first step was the virtually quantitative [12, 13] pyrolysis of the esters at 600° in a stream of purified, oxygen-free, dry nitrogen into benzoic acid and a mixture of unsaturated hydrocarbons, a pyrolysing unit being used similar to that employed by Bender.[13] The decomposition products collected in the liquid-air trap appeared to be a mixture of hydrocarbons and benzoic acid. The second step consisted in preparing and decarboxylating silver benzoate (see above).

The reliability of this method was tested as follows: 1-Phenylallyl benzoate (0·576M) and labelled benzoic acid (0·484M) were heated in chlorobenzene until the extinction coefficient at 250 mμ of the mixed isomers rose from 2080 to 17,700. During the same period the enrichment of benzoic acid in ^{18}O atoms % excess above normal, β′, decreased from 1·96 to 1·156. After extraction of the benzoic acid, the purified ester mixture (ε 17,700) was pyrolysed (β′ = 0·662). The expected enrichment $\beta' = (1{\cdot}96 - 1{\cdot}156)0{\cdot}484/0{\cdot}576 = 0{\cdot}674$.

The author is indebted to Professor E. D. Hughes, F.R.S., and Sir Christopher Ingold, F.R.S., for helpful discussions, to Professor D. R. Llewellyn for a generous gift of ^{18}O-enriched water, and to Dr. C. A. Bunton for all the mass-spectrometric analyses.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1. [*Received, May 30th*, 1958.]

[12] Biltger and Hibbert, *J. Amer. Chem. Soc.*, 1936, **58**, 823.
[13] Bender, *ibid.*, 1951, **73**, 1626.

---

879. *Reactivities of Aromatic Hydrocarbons. Part I. Bromination.*

By S. F. MASON.

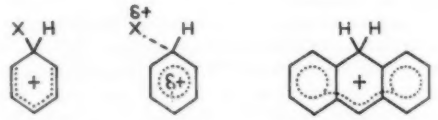
Reaction of molecular bromine in 85% acetic acid at 25° with benzene, diphenyl, and naphthalene is shown to be nearly of the third order. Under the same conditions that of phenanthrene is nearly of the second order, owing to the predominance of addition over substitution. The relative reactivities of benzene, diphenyl, and naphthalene, which cover a range of $>10^5$, are proportional to the atom localisation energies of the most reactive positions in these molecules, the correlation giving an apparent β value of −29 kcal./mole for bromination. The significance of the β values for a number of aromatic substitutions is discussed in relation to a limiting β value derived from the relative ionisation constants of the aromatic hydrocarbons.

IT has been shown that the free energies of activation ($\Delta G^{\ddagger}$) for electrophilic [1,2] and free-radical [1,3] substitution in a series of aromatic hydrocarbons are linearly proportional to the atom localisation energies ($E_L\beta^{-1}$) of the most reactive position in the hydrocarbon, and that the relative free energies of substitution in the various positions of a polycyclic aromatic nucleus give a similar correlation with the $E_L\beta^{-1}$ values of these positions.[1] The atom localisation energy of a given position in an aromatic hydrocarbon, which is the difference in π-electron energy between the hydrocarbon (*e.g.*, benzene) and the corresponding Wheland intermediate [4] (*e.g.*, I), is obtained [5] in terms of the empirical carbon–carbon resonance integral (β), which, from the resonance energies of the aromatic hydrocarbons, has the value of about −20 kcal./mole in the Hückel approximation.[6] From the gradients of the correlations between $\Delta G^{\ddagger}$ and $E_L\beta^{-1}$ in a series of hydrocarbons apparent β values for a number of substitution reactions have been derived.[1-3] In a number of cases the apparent β values are smaller than the Hückel value, from which it has been inferred [1] that

[1] Dewar, Mole, and Warford, *J.*, 1956, 3581.
[2] Dewar and Mole, *J.*, 1957, 342.
[3] Coulson, *J.*, 1955, 1435.
[4] Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900.
[5] Burkitt, Coulson, and Longuet-Higgins, *Trans. Faraday Soc.*, 1951, **47**, 553.
[6] Coulson, "Valence," Oxford University Press, 1952, p. 240.

XUM

the Wheland intermediate (*e.g.*, I) is only partly formed (*e.g.*, II) in the transition state for aromatic substitution. The linear relations between $\Delta G^{\ddagger}$ and $E_L\beta^{-1}$, and the different apparent β values, are then accounted for if it is assumed that the degree to which the intermediate is formed in the transition state is constant in a series of hydrocarbons for a given reaction, but varies from one substituting reagent to another.



(I) (II) (III)

The apparent β values for the various reaction-series increase with the selectivity of the attacking reagent for substitution at the most reactive position in a given aromatic compound,[1,2] from which it may be supposed that the transition state for substitution more nearly resembles the intermediate the greater the selectivity of the attacking reagent. On the basis of Hückel localisation energies,[5] some apparent β values are −7 kcal./mole for the attack of methyl radicals,[3] −16 kcal./mole for the attack of trichloromethyl radicals,[7] nitration,[1] and hydrogen–deuterium exchange,[8] and, for chlorination,[2] −28 and −36 kcal./mole for substitution in acetic acid and in 3 : 1 carbon tetrachloride–acetic acid respectively. No particular significance attaches to the β values larger than the Hückel value, as simple molecular-orbital theory does not give a good quantitative account of odd alternant systems.[9] However, according to the theory presented, an empirical upper limit to the apparent β values derived from aromatic substitutions should be provided by measurements of the basicity of aromatic hydrocarbons.[10] In strong acid solution anthracene gives a cation which is known [11] to have the structure (III), whilst for the " benzenium " the structure (I; X = H) is likely, [12,13] and, in general, the cations formed by the simpler aromatic hydrocarbons in strong non-oxidising acids [14] probably have the structures of the corresponding Wheland intermediates.[10–14] The ionisation constants of the aromatic hydrocarbons in anhydrous hydrofluoric acid [10] give linear correlation with the Hückel atom localisation energy of the most reactive position in the nucleus (curve *A* of the Figure), and from the slope of the line an apparent β value of −35 kcal./mole is obtained.[10] The entropy of ionisation does not vary in the series of aromatic hydrocarbons studied,[15] and if, in aromatic substitution, the entropy of activation is approximately constant from one hydrocarbon to another, *ca.* −35 kcal./mole should represent an approximate empirical upper limit for apparent β values derived from rate studies. Moreover, the ratio of the particular β value for a given reagent to the limiting value should afford a rough index of the degree to which the transition state in an aromatic substitution resembles the Wheland intermediate, provided that the degree of formation of the latter in a series of aromatic hydrocarbons is constant with a given substitution reagent.

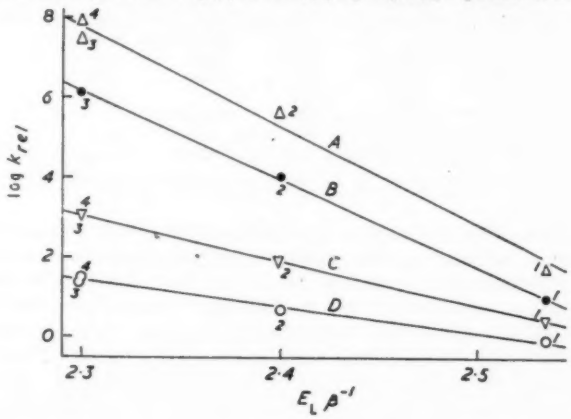
In view of the observed increase in the apparent β values with the orientational selectivity of the attacking reagent, and the attainment of the empirical maximum in one of the chlorinations, it appeared of interest to obtain a β value for the most selective electrophilic aromatic substitution reagent yet known, molecular bromine.[16] Accordingly,

[7] Kooyman and Farenhorst, *Trans. Faraday Soc.*, 1953, **49**, 58.
[8] Dallinga, Verrijn, Stuart, Smit, and Mackor, *Z. Elektrochem.*, 1957, **61**, 1019.
[9] Brickstock and Pople, *Trans. Faraday Soc.*, 1954, **50**, 901.
[10] Mackor, Hofstra, and van der Waals, *ibid.*, 1958, **54**, 66.
[11] Gold and Tye, *J.*, 1952, 2172.
[12] Reid, *J. Amer. Chem. Soc.*, 1954, **76**, 3264.
[13] Muller, Pickett, and Mulliken, *J. Amer. Chem. Soc.*, 1954, **76**, 4770.
[14] MacLean and van der Waals, *J. Chem. Phys.*, 1957, **27**, 827.
[15] Mackor, Hofstra, and van der Waals, *Trans. Faraday Soc.*, 1958, **54**, 186.
[16] Brown and Stock, *J. Amer. Chem. Soc.*, 1957, **79**, 1421.

XUM

the relative reactivities of benzene, diphenyl, naphthalene, and phenanthrene towards molecular bromine in 85% acetic acid have now been measured. The kinetics of the reaction between molecular bromine and aromatic hydrocarbons are complex,[17,18] but the relative reactivities of a number of benzene derivatives with bromine in acetic acid have been obtained from the time required to achieve a given percentage of reaction under a standardised set of conditions.[16,17,19,20] This method was employed in the present study, the conditions adopted being given by the following considerations. In glacial acetic acid the reaction between bromine and benzene is very slow at 25°, whilst naphthalene in the same circumstances gives reaction kinetics nearly of the fourth order.[17,18] In 85% acetic acid, however, the rate of reaction between bromine and benzene at 25° becomes measurable, the kinetics given by a number of benzene derivatives being approximately

The relations between the atom localisation energy ($E_L\beta^{-1}$) and the logarithms of (A) the relative ionisation constants,[10] (B) the relative rates of bromination, (C) the relative rates of nitration,[1] and (D) the relative rates of reaction with methyl radicals [2] of (1) benzene, (2) diphenyl, (3) naphthalene, and (4) phenanthrene.



of the third order,[16,17] and there were indications that naphthalene under the same conditions would give third-order kinetics over a certain concentration range.[17,18]

At the concentrations studied, and under the above conditions, it is found (Table) that benzene, diphenyl, and naphthalene react approximately according to a third-order kinetic law. The reaction of phenanthrene is, however, very nearly of the second order (Table), probably owing to the predominance of the 9 : 10-addition of bromine over nuclear substitution, so that little or no hydrobromic acid is formed to remove bromine as the tribromide ion or hydrogen tribromide and thus to increase the order with respect to bromine.[21] Only the relative reactivities of benzene, diphenyl, and naphthalene, based on the times required for 5 and 10% reaction, are, therefore, comparable. The relative reactivities cover a range of greater than 10^5 (Table), and the relative free energies of activation are found to increase with the atom localisation energies of the most reactive positions of the three hydrocarbons (plot *B*), the slope of the relation giving an apparent β value of about −29 kcal. mole for aromatic substitution with molecular bromine in 85% acetic acid.

The apparent β values for aromatic substitution with molecular halogens are large in relation to the empirical limiting value, suggesting that the Wheland intermediate is almost

[17] Robertson, de la Mare, and Johnston, *J.*, 1943, 276.
[18] de la Mare and Robertson, *J.*, 1948, 100.
[19] Robertson, de la Mare, and Swedlund, *J.*, 1953, 782.
[20] de la Mare and Vernon, *J.*, 1951, 1764.
[21] Robertson, *J.*, 1954, 1267.

XUM

completely formed in the transition states for these reactions. It has been argued [22] that the absence of an isotope effect in aromatic nitration and bromination [23] demonstrates that the transition state in electrophilic substitution cannot resemble the Wheland intermediate, since there should be a marked fall in zero-point energy when the C–H bond of the carbon atom under attack changes from sp^2 to sp^3 hybridisation. Although the stretching frequency of a C–H bond falls with such a change of hybridisation, the deformation frequencies rise, and the overall energy change is small, the calculated zero-point energies being 2400 and 2367 cm.$^{-1}$ for sp^2 and sp^3 C–H bonds respectively.[23]

The times required for 5% *and* 10% *reaction between benzene, diphenyl, naphthalene, and phenanthrene with bromine in* 85% *acetic acid at* 25°. *The orders of the reaction* (n), *the relative reactivities* (R) *of the hydrocarbons, and the atom localisation energies of the most reactive position in the hydrocarbon* ($E_L\beta^{-1}$).

Hydrocarbon	[ArH] (molar)	[Br_2] (molar)	T (5%) (min.)	T (10%) (min.)	n	R	$E_L\beta^{-1}$ [b]
Benzene	0·45	0·0425	—	77,000 [a]	~3	1	2·536
	0·60	0·06	19,000	44,000			
Diphenyl	0·10	0·01	610	1350	3·05	$1·1 \times 10^3$	2·400
	0·167	0·0167	215	460			
Naphthalene	0·04	0·005	23·5	51	2·95	$1·4 \times 10^5$	2·299
	0·08	0·01	6·0	13·5			
Phenanthrene	0·01	0·002	9·0	21	2·12	—	2·299
	0·02	0·004	20	47			

[a] Quoted from ref. 16. [b] Quoted from Part II (to follow).

The absence of an isotope effect in bromination and nitration is consistent with the theory of aromatic substitution presented above, but there are other aspects of the theory which are less satisfactory. In electrophilic substitution with molecular halogens the reactants are neutral species,[21] and the formation of a transition state resembling the Wheland intermediate requires the separation of charge. The apparent β values for chlorination suggest that the transition state more nearly resembles the intermediate in 3 : 1 carbon tetrachloride–acetic acid than in acetic acid solution, which leads to the unsatisfactory conclusion that the separation of charge in the transition state is larger in the solvent of lower ionising power. Again, bromination in aqueous acetic acid and chlorination in glacial acetic acid give nearly the same apparent β values, though bromine is the more selective reagent and aqueous acetic acid the solvent of higher ionising power.

For substitutions of a series of aromatic hydrocarbons it is probable that there are major variables other than the atom localisation energy of the position attacked, notably, the solvation energy of the transition state. For electrophilic substitution the Wheland intermediate is an odd alternant carbonium ion with the positive charge dispersed over the starred atoms. The spread of the charge varies in a determinate manner from one intermediate to another, and the solvation energy of the intermediate, particularly that due to the charging process,[24] should vary likewise in a series of aromatic hydrocarbons. The influences of the atom localisation energy and the solvation energy of the transition state upon the course of electrophilic substitution may be distinguished in principle, as the former is an internal-energy and the latter a free-energy term. The temperature gradient of the solvation energy should, therefore, give rise to a difference in the entropy of activation between one hydrocarbon and another in a reaction with a given reagent. The differences should be most marked with a reaction in which the Wheland intermediate is the most completely formed in the transition state, namely, in a reaction with a reagent of high orientational selectivity. Although molecular bromine is the most selective reagent for substitution, the kinetic complexities of bromination do not allow the entropies of

[22] Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.
[23] Melander, *Arkiv Kemi, Min., Geol.*, 1950, **2**, 211.
[24] Mason, *J.*, 1958, 808.

XUM

activation to be measured at all readily, and the supervention of addition limits the range of hydrocarbons which may be studied. Accordingly, chlorination in acetic acid was chosen for the investigation of the entropies of activation in aromatic substitution, which it is hoped to describe subsequently.

Experimental

Acetic acid was treated by standard methods [17-20] and had m. p. 16·5°. "AnalaR" bromine was used without further purification. "AnalaR" benzene was dried (Na) and fractionated, the middle portion, b. p. 80°, being collected. Naphthalene was of an analytical grade, and phenanthrene was purified by treatment with maleic anhydride.[2] After recrystallisation, diphenyl had m. p. 70°, and phenanthrene m. p. 100°.

Rate Measurements.—These were carried out by standard methods,[16, 20] sealed tubes being used, in conjunction with controls, in the case of benzene, and brown bottles for the polycyclic hydrocarbons. To avoid losses by evaporation, the bottles were filled and not more than three samples were taken from any one bottle. The reactions were followed by pipetting 5—10 c.c. samples into excess of 5% potassium iodide solution and titrating these mixtures against 0·05—0·002N-sodium thiosulphate. The percentage of reaction was plotted against time, and the 5% and the 10% intercept were noted.

The University, Exeter. [*Received, June 20th*, 1958.]

---

880. *Pavine. Part III.* Related Synthetic Work.*

By A. R. Battersby and R. Binks.

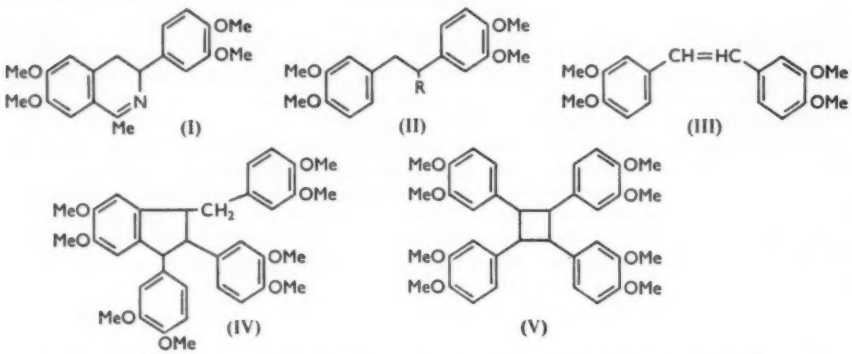
The action of phosphoric oxide on *N*-acetyl-1 : 2-bis-(3 : 4-dimethoxyphenyl)ethylamine in boiling toluene yields, not the expected 3 : 4-dihydro-*iso*quinoline (I), but a dimer of 3 : 4 : 3′ : 4′-tetramethoxystilbene, which can be obtained directly from 3 : 4 : 3′ : 4′-tetramethoxystilbene under the same conditions. The 1 : 2 : 3 : 4-tetrahydro*iso*quinoline (VI) results from attempted methylation of 1 : 2-bis-(3 : 4-dimethoxyphenyl)ethylamine (II; R = NH_2) with formaldehyde and formic acid; when the latter base reacts with acetaldehyde and sulphuric acid, the 1 : 2 : 3 : 4-tetrahydro-1-methyl-*iso*quinoline (VII) is obtained. This is dehydrogenated in good yield by mercuric acetate to give the corresponding 3 : 4-dihydro-1-methyl*iso*-quinoline (I). Other related experiments are described.

In connection with work on pavine [1] and 1 : 2-dihydro*iso*quinolines,[2] we wished to synthesise the 3 : 4-dihydro*iso*quinoline (I). The obvious route is by Bischler–Napieralski ring-closure of the amide (II; R = NHAc) for which the necessary starting material is the amine (II; R = NH_2). This had previously been prepared [3] by reducing the oxime of 3 : 4 : 3′ : 4′-tetramethoxydeoxybenzoin, but is now available more conveniently in 63% yield by use of Leuckart's reaction. When the derived acetyl derivative (II; R = NHAc) was heated in toluene with phosphoric oxide or phosphorus oxychloride, a trace of crude basic material was obtained together with a nitrogen-free neutral product, m. p. 155—156°. It seemed probable that the latter was the known 3 : 4 : 3′ : 4′-tetramethoxystilbene (III), which has a m. p. reported [4] in the range 153—156°; examples are avilable [5] of the elimination of acylamide from acyl derivatives of 1 : 2-diarylethylamines under the influence of hot phosphoric oxide. The analysis of the neutral product was in agreement with this, but the substance was unaffected by hydrogenation in acetic acid over platinum

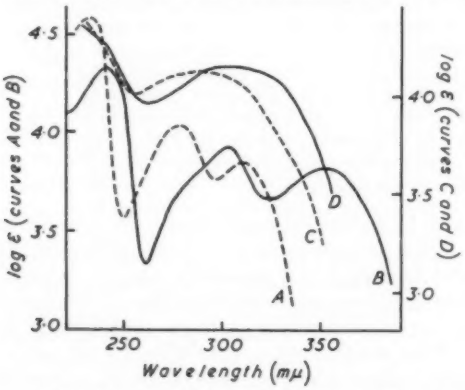
* Part II, *J.*, 1958, 1988.

[1] Battersby and Binks, *J.*, 1955, 2888.
[2] Battersby, Binks, and Uzzell, *Chem. and Ind.*, 1955, 1039.
[3] Buck and Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 310.
[4] Feuerstein, *Ber.*, 1901, **34**, 415; Richtzenhain and von Hofe, *Ber.*, 1939, **72**, 1890; Wood, Bacon, Meibohm, Throckmorton, and Turner, *J. Amer. Chem. Soc.*, 1941, **63**, 1334.
[5] Cook, Dickson, Ellis, and Loudon, *J.*, 1949, 1074.

and its ultraviolet absorption confirmed the absence of conjugated olefinic and veratrole residues. Determination of its molecular weight showed that the neutral product is a dimer of the stilbene (III) initially produced in the reaction and a number of structures is possible for this product, for example, the indane (IV), based upon that of anethole dimer,[6] or the *cyclo*butane (V).



In extension of the foregoing work 3 : 4 : 3′ : 4′-tetramethoxystilbene (III) was made by Hofmann degradation of the methiodide of the base (II; R = NMe_2). A simpler route to the stilbene (III) involves acid-catalysed dehydration of the alcohol (II; R = OH) resulting from the hydrogenation of 3 : 4 : 3′ : 4′-tetramethoxydeoxybenzoin. When the stilbene (III) was heated in toluene with phosphoric oxide, it afforded the dimer which had been isolated earlier from the attempted Bischler–Napieralski reaction.



Ultraviolet absorption spectra in ethanol of:
(*A*) *the* 3 : 4-*dihydro*isoquinoline (I).
(*B*) *the* 3 : 4-*dihydro*isoquinoline (I) *as the hydrogen oxalate.*
(*C*) *the dimethylaminomethylstilbene derivative* (IX).
(*D*) 3 : 4 : 3′ : 4′-*tetramethoxystilbene* (III).

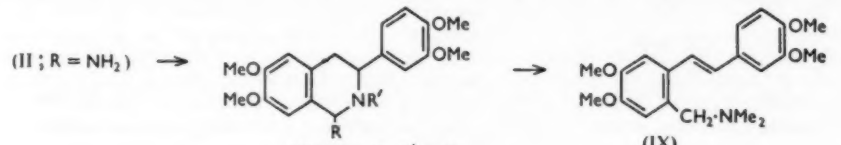
After the completion of this work, the action of phosphorus oxychloride on the amide (II; R = NHAc) was described [7] as yielding the stilbene (III). Dr. Walker has very kindly compared his material with our sample of the dimer by mixed m. p. and by infrared absorption, and the two products are identical.

Before the successful preparation of the methiodide (II; R = $NMe_3^+I^-$), the action of formic acid and formaldehyde on the base (II; R = NH_2) was examined with the aim of preparing the tertiary amine (II; R = NMe_2), $C_{20}H_{27}O_4N$. The product, $C_{20}H_{25}O_4N$, yielded a methiodide which underwent Hofmann degradation to a base, $C_{21}H_{27}O_4N$, having one double bond (micro-hydrogenation) and an ultraviolet absorption spectrum very similar to that of 3 : 4 : 3′ : 4′-tetramethoxystilbene (Figure). These results are

[6] Baker and Enderby, *J.*, 1940, 1094.
[7] Walker, *J. Amer. Chem. Soc.*, 1954, **76**, 3999.

interpreted in the following scheme in which the first step is an example where a Pictet–Spengler ring closure is preferred to *N*-dimethylation.[8]

The differences observed in the absorption spectra of the two stilbene derivatives are no doubt due to the steric effect [9] of the $CH_2 \cdot NMe_2$ group in the base (IX).



(VI): R = H, R′ = Me
(VII): R = Me, R′ = H
(VIII): R = R′ = Me

(IX)

The ease of formation of the tetrahydro*iso*quinoline (VI) suggested the acid-catalysed condensation of acetaldehyde with the amine (II; R = NH_2) which gave the tetrahydro-*iso*quinoline (VII) in 74% yield together with a small amount of the stilbene (III); the formation of the latter emphasises the ease with which elimination occurs in this series. The base (VII) showed only very weak infrared absorption in the NH stretching region, but doubts about the secondary nature of the nitrogen atom were removed by the preparation, in high yield, of the neutral acetyl derivative of (VII) which had the expected strong band at 1655 cm.$^{-1}$ (–CO·NRR′). There have been a few other examples of piperidine derivatives which show weak or negligible NH stretching absorption.[10]

Dehydrogenation of the base (VII) with mercuric acetate gave 71% of a base, $C_{20}H_{23}O_4N$, having an ultraviolet absorption (Figure) identical with that obtained by summing the absorptions of 4-alkylveratrole and 3 : 4-dihydro-6 : 7-dimethoxy-1-methyl-*iso*quinoline. The ultraviolet absorption also underwent the expected bathochromic shift when the nitrogen was protonated. This product is therefore the required 3 : 4-dihydro-*iso*quinoline (I) and confirmation was obtained when the infrared spectrum of this base showed bands at 1622, 1606, and 1573 cm.$^{-1}$, a group which is characteristic of this type of 3 : 4-dihydro*iso*quinoline.[11] That no rearrangement of the skeleton had occurred during dehydrogenation was shown by reducing the base (I) catalytically to the tetrahydro*iso*-quinoline (VII).

Leonard and his co-workers [12] have recently studied the action of mercuric acetate on simple quinolizidines and piperidines, but the dehydrogenation of simple tetrahydro*iso*-quinolines by this reagent has not previously been examined. The result obtained here has, besides its general interest as a mild method for converting 1 : 2 : 3 : 4-tetrahydro- into the corresponding 3 : 4-dihydro-*iso*quinolines, also that of serving as a model for the first stage in the dehydrogenation of emetine by mercuric acetate.[13]

The preparations of the tetrahydro-2-methyl*iso*quinoline (VIII) and the corresponding methiodide are described in the Experimental section.

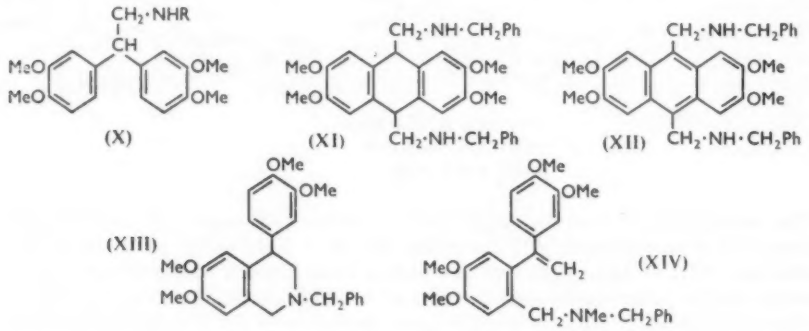
Other model experiments related to work on *iso*pavine [14] required the preparation of a base of the type (X). Veratrole condensed with *N*-benzyl-2 : 2-dimethoxyethylamine, to give a mixture of bases from which the ethylamine (X; R = CH_2Ph) and the dihydro-anthracene (XI) were isolated by fractional crystallisation of the picrates. The picrate of the base (XI) was stable, but the free base gradually changed and, after being dried at 100°, was shown by its ultraviolet absorption to contain about 10% of the corresponding

[8] Cf. Castrillon, *ibid.*, 1952, **74**, 558; Baltzly, *ibid.*, 1953, **75**, 6038.
[9] Braude, *Experientia*, 1955, **11**, 457.
[10] Marion, Ramsay, and Jones, *J. Amer. Chem. Soc.*, 1951, **73**, 305.
[11] Battersby, Davidson, and Harper, forthcoming publication.
[12] Leonard and Hauck, *J. Amer. Chem. Soc.*, 1957, **79**, 5279, and earlier papers.
[13] Battersby and Openshaw, *J.*, 1949, S 67.
[14] Battersby and Yeowell, *J.*, 1958, 1988.

XUM

anthracene (XII). This ready aromatisation of 9 : 10-dihydroanthracenes has been encountered previously.[15]

When the base (X; R = CH_2Ph) was methylated with formic acid and formaldehyde, a ring-closure occurred similar to that discussed above. The product was shown to be the tetrahydro*iso*quinoline (XIII) by analysis of its crystalline methiodide and by Hofmann



degradation of the latter to an unsaturated basic gum (XIV) having ultraviolet absorption almost identical with that of a related compound (compound VI; R = H in Part II [14]). The infrared spectrum of the base (XIV) had absorption bands at 885, 1303, 3075 cm.$^{-1}$ (>C=CH_2) in keeping with the proposed structure.

Experimental

Analytical samples were dried at 100° *in vacuo* over phosphoric oxide unless otherwise stated.

1 : 2-*Bis*-(3 : 4-*dimethoxyphenyl*)*ethylamine* (II; R = NH_2).—A mixture of 3 : 4 : 3′ : 4′-tetramethoxydeoxybenzoin (25 g.), ammonium formate (50 g.), and 90% formic acid (10 ml.) was heated in a modified Claisen flask, the temperature being raised from 150—180° at such a rate that the foaming was under control, and then held at 185° for 3 hr. The cooled product was partitioned between water (200 ml.) and benzene (1 l.), and the product recovered by evaporation of the benzene was heated under reflux for 1½ hr. with aqueous 5N-sulphuric acid (150 ml.). The cooled solution was extracted with ether (3 × 200 ml.), and the aqueous layer was made strongly alkaline. The precipitated base crystallised from water to give the ethylamine derivative (15·9 g., 63%), m. p. 107°; its *N*-acetyl derivative prepared in the usual way had m. p. 161—162°. Buck and Allen [3] report m. p. 107° and 160—162° respectively for these compounds.

Attempted Cyclisation of N-*Acetyl*-1 : 2-*bis*-(3 : 4-*dimethoxyphenyl*)*ethylamine* (II; R = NHAc).—A solution of the *N*-acetyl derivative (0·8 g.) in dry boiling toluene was treated with dry " Filtercel " (2 g.) and phosphoric oxide (2 g.). Further portions (2 g.) of phosphoric oxide were added after 15 min. and 30 min. and the total time of heating was 1 hr. The cooled suspension was poured on ice and then filtered. After the filter pad had been washed with hot toluene, the filtrate was separated into aqueous and organic layers. The latter was shaken with an excess of aqueous hydrochloric acid, and the aqueous extract was added to the main aqueous solution which was then extracted thrice with ethyl acetate. The toluene and ethyl acetate solutions were combined, dried, and evaporated to give the neutral fraction (0·579 g.). After being made strongly alkaline with potassium hydroxide, the aqueous layer was extracted thrice with ether which removed a brown gum (31 mg.).

Crystallisation of the neutral fraction from ethanol gave the *dimer* (0·244 g.), m. p. 155—156°, of 3 : 4 : 3′ : 4′-tetramethoxystilbene [Found: C, 71·5; H, 6·6%; *M* (in camphor), 500. $C_{36}H_{40}O_8$ requires C, 72·0; H, 6·7%; *M*, 600]. Five molecular-weight determinations in

[15] Müller, Raltschewa, and Papp, *Ber.*, 1942, **75**, 692.

camphor on a veratrole derivative of unequivocal structure (compound I; R = CH_2·NMe_2; ref. 13) all gave results 17—25% low. The m. p. of the dimer was depressed to 130—142° in admixture with 3 : 4 : 3′ : 4′-tetramethoxystilbene prepared as below.

The same dimer was obtained when phosphorus oxychloride (1 ml.) replaced the phosphoric oxide in the above experiment.

1 : 2-*Bis*-(3 : 4-*dimethoxyphenyl*)*ethyltrimethylammonium Iodide*.—Methyl iodide (6 ml.) was heated for 10 hr. under reflux with a solution of 1 : 2-bis-(3 : 4-dimethoxyphenyl)ethylamine (1 g.) and anhydrous sodium carbonate (0·5 g.) in water (30 ml.) and purified dioxan (45 ml.). Addition of aqueous sodium thiosulphate to the cooled solution removed the iodine, and the solution was then evaporated until free from dioxan and methyl iodide. The resulting suspension was extracted thrice with ether–chloroform (10 : 1) which removed a solid (0·1 g.) crystallising from ethanol as needles (30 mg.), m. p. 117—118°.

The aqueous alkaline layer was acidified, treated with potassium iodide (10 g.), and extracted thrice with chloroform. Evaporation of the dried extract at 40° left crystals which, when recrystallised from ethanol, gave the *iodide* as rods (1·38 g., 89%), m. p. 179—180° (decomp.) unchanged by further recrystallisation (Found: C, 51·4; H, 6·4; I, 26·2. $C_{21}H_{30}O_4NI$ requires C, 51·7; H, 6·2; I, 26·4%).

3 : 4 : 3′ : 4′-*Tetramethoxystilbene* (III).—(*a*) A solution of the foregoing methiodide (0·8 g.) in warm water (40 ml.) was shaken for 30 min. with moist silver oxide (from 2 g. of silver nitrate), then filtered. The filtrate and washings (total 100 ml.) were treated with sodium hydroxide (80 g.), heated under reflux for 2 hr., then cooled and extracted thrice with ether. Evaporation of the dried ethereal solution left the stilbene as plates (0·45 g., 92%), m. p. 153—154° (from ethanol) (Found: C, 72·1; H, 6·5. Calc. for $C_{18}H_{20}O_4$: C, 72·0; H, 6·7%). Hydrogenation of this product in ethanol over platinum at 17°/751 mm. (uptake 1·06 mol.) gave 3 : 4 : 3′ : 4′-tetramethoxydibenzyl, m. p. and mixed m. p. 108—109°.

(*b*) When 3 : 4 : 3′ : 4′-tetramethoxydeoxybenzoin (1 g.) in ethanol (150 ml.) was shaken at 20°/758 mm. with hydrogen and 10% palladised charcoal, gas was absorbed (1 mol.) during 5 hr. The solution was filtered and evaporated to dryness to leave a crystalline residue. Part of this (0·3 g.) was heated under reflux with aqueous 2N-sulphuric acid (15 ml.) for 7 hr.; on cooling, crystals separated. These were recrystallised from ethanol to afford the stilbene (III), m. p. 152—154°, alone or on admixture with the sample from (*a*) above, $\lambda_{min.}$ 261 (log ε 3·95), $\lambda_{max.}$ 303 mμ (log ε 4·14) in EtOH.

Dimerisation of 3 : 4 : 3′ : 4′-*Tetramethoxystilbene*.—The stilbene (0·2 g.) in dry toluene (20 ml.) was heated under reflux for 8 hr. with phosphoric oxide (2 g.) which had been exposed to the air for *ca.* 1 min. The mixture was worked up as described above for the isolation of the neutral fraction in the attempted cyclisation. A gum was obtained which crystallised from ethanol to give the stilbene dimer (50 mg.), m. p. 153—156°, alone or on admixture with the product from the attempted cyclisation, but depressed to 133—140° when mixed with the stilbene (III).

3-(3 : 4-*Dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-*methylisoquinoline* (VI) *and its Methiodide*.—1 : 2-Bis-(3 : 4-dimethoxyphenyl)ethylamine (1 g.) was heated at 100° for 8 hr. with 95% formic acid (5 ml.) and 37% aqueous formaldehyde (5 ml.), and the solution then poured into water and made alkaline. The precipitated base was extracted into ether–chloroform (10 : 1) and recovered from the dried solution by evaporation. Crystallisation from aqueous ethanol (30% ethanol by vol.) gave the *tetrahydroisoquinoline* (0·92 g.), m. p. 123—125° (Found: C, 69·9; H, 7·3; N, 4·3. $C_{20}H_{25}O_4N$ requires C, 69·95; H, 7·3; N, 4·1%).

A solution of this base (0·5 g.) in ether (20 ml.), methanol (5 ml.), and methyl iodide (5 ml.) was kept in the dark for 44 hr. The precipitated solid (0·7 g.) was washed with ether and recrystallised from aqueous ethanol, to give the *methiodide*, m. p. 250—252° (decomp.) (Found: C, 52·1; H, 5·9; I, 26·9. $C_{21}H_{28}O_4NI$ requires C, 52·0; H, 5·8; I, 26·2%).

Hofmann Degradation of 3-(3 : 4-*Dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2 : 2-*dimethylisoquinolinium Iodide*.—The foregoing methiodide (0·412 g.) was degraded as for the preparation of the stilbene (III) above, by using water (30 ml.), silver nitrate (0·5 g.), potassium hydroxide (20 g.), and a period of reflux of 5 hr. The products were separated into a neutral (16 mg.) and a basic fraction (240 mg.) in the usual way. The latter crystallised from aqueous ethanol to give 2-*dimethylaminomethyl*-4 : 5 : 3′ : 4′-*tetramethoxystilbene* (IX) as stout prisms (0·17 g.), m. p. 101—103° (Found in material dried at 78°: C, 70·7; H, 7·6; N, 4·2. $C_{21}H_{27}O_4N$ requires C, 70·6; H, 7·6; N, 3·9%), $\lambda_{min.}$ 254 (log ε 4·0), $\lambda_{max.}$ 289 mμ (log ε 4·12) in EtOH.

XUM

This base (20·6 mg.) was hydrogenated in ethanol at 18°/743 mm. over platinum; uptake of hydrogen (1·03 mol.) ceased after 2 hr.

3-(3 : 4-*Dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*isoquinoline (VII).—To a solution of 1 : 2-bis-(3 : 4-dimethoxyphenyl)ethylamine (3 g.) in aqueous 6N-sulphuric acid (120 ml.) was added acetaldehyde (9 ml.), and the mixture was heated under reflux for 1 hr. A second portion (9 ml.) of acetaldehyde was added to the cooled solution which was then kept overnight. After addition of more acetaldehyde (6 ml.) next day, the solution was heated under reflux for 5 hr. Extraction of the tarry solution with ether removed a solid which crystallised from ethanol as colourless plates (0·28 g.), m. p. 151—152°, raised to 152—153° on admixture with the tetramethoxystilbene (III).

The main aqueous solution was made strongly alkaline with potassium hydroxide and extracted thrice with ether; evaporation of the dried extract left a crystalline residue. This was recrystallised from ether, to give the *tetrahydroisoquinoline* as plates (2·38 g., 74%), m. p. 125—128°, raised to 130—133° by repeated recrystallisation from aqueous ethanol (Found: C, 70·1; H, 7·5; N, 3·9. $C_{20}H_{25}O_4N$ requires C, 69·9; H, 7·3; N, 4·1%), $\lambda_{min.}$ 222 and 253, $\lambda_{max.}$ 229 and 281 mμ (log ε 4·18, 2·83; 4·2, 3·82 respectively) in EtOH.

When the tetrahydro*iso*quinoline (41 mg.) was heated on the steam-bath for 2 hr. with acetic anhydride (1 ml.), and the reaction mixture then worked up as usual for neutral material, the *N*-acetyl derivative was obtained as a colourless resin (45 mg., 98%).

3-(3 : 4-*Dimethoxyphenyl*)-3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-*methyl*isoquinoline (I).—A solution of the foregoing base (2·2 g.) in water (35 ml.) and acetic acid (3·5 ml.) was treated with mercuric acetate (10 g.) and warmed gently until a clear solution was obtained. This was heated under reflux for 9 hr., then cooled and filtered, the mercurous acetate being washed with water and ethanol. Hydrogen sulphide was passed for 10 min. at 55° through the aqueous-alcoholic solution, which was then acidified with aqueous 2N-hydrochloric acid (25 ml.) and treated again with hydrogen sulphide for 1 hr. After coagulation of the precipitate so formed by heat, the solution was filtered and the filter pad was washed with hot water (3 × 30 ml.) and boiling ethanol (3 × 30 ml.), both solvents having been acidified with a few drops of 2N-hydrochloric acid. The combined filtrates and washings were evaporated until free from ethanol, then extracted thrice with ether, and the extracts were rejected. The aqueous layer was made strongly alkaline with potassium hydroxide and extracted with ether (3 × 100 ml.) which removed a crystalline base (1·85 g.). A solution of this base in ethanol was treated with a saturated solution of hydrated oxalic acid (1·5 g.) in ethanol, yielding a pasty precipitate. This crystallised well from ethanol (1·2 l.), to afford the *dihydroisoquinoline hydrogen oxalate* (cf. I) as fine needles (2·02 g.), m. p. 217° (decomp.), raised to 219° (decomp.) by further recrystallisation from ethanol (Found: C, 61·0; H, 5·9; N, 3·5. $C_{22}H_{25}O_8N$ requires C, 61·2; H, 5·8; N, 3·2%), $\lambda_{min.}$ 220, 261, and 323, $\lambda_{max.}$ 241, 303, and 352 mμ (log ε 4·10, 3·32, 3·66; 4·33, 3·93, 3·83) in EtOH. The *base* (I), recovered from the hydrogen oxalate by treatment with aqueous alkali and extraction with ether, crystallised from aqueous ethanol as prismatic needles (1·55 g., 71% overall), m. p. 115—116° (Found: C, 70·8; H, 6·8; N, 4·3. $C_{20}H_{23}O_4N$ requires C, 70·4; H, 6·8; N, 4·1%), $\lambda_{min.}$ 249 and 296, $\lambda_{max.}$ 231, 278, and 310 mμ (log ε 3·56, 3·76; 4·58, 4·04, 3·85 respectively) in EtOH.

A sample (23·6 mg.) of this base was hydrogenated in ethanol (5 ml.) in the presence of platinum (10 mg.) at 19°/747 mm. Hydrogen (1·0 mol.) was absorbed for 12 min. and uptake then ceased. The product, isolated in the usual way, had m. p. 127—128°, raised to 130—133° on admixture with the tetrahydro*iso*quinoline (VII).

3-(3 : 4-*Dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1 : 2-*dimethyl*isoquinoline *and its Methiodide*.—A solution of the tetrahydro*iso*quinoline (VII) (0·2 g.) in 95% formic acid (4 ml.) and aqueous formaldehyde (8 ml.) was heated at 100—110° for 15 hr., then poured into aqueous 0·1N-hydrochloric acid (20 ml.). After extraction thrice with ether, the aqueous solution was made alkaline with sodium hydroxide and extracted thrice again with ether. Evaporation of the dried second set of ether-extracts left a gum which yielded the crystalline *perchlorate* (0·25 g.) of the tetrahydro-2-methyl*iso*quinoline (VIII). Recrystallised from aqueous ethanol, this had m. p. 211—212° (Found: C, 55·5; H, 6·4. $C_{21}H_{28}O_8NCl$ requires C, 55·1; H, 6·2%).

The tertiary base (VIII), recovered as usual from the perchlorate, was dissolved in dry ether and kept with an excess of methyl iodide overnight. The crystals which separated were recrystallised from ethanol to give the *methiodide*, m. p. 170°, with gas evolution to a resin which flows at 208—209° (decomp.) (Found: C, 52·8; H, 6·2. $C_{22}H_{30}O_4NI$ requires C, 53·0;

XUM

H, 6·1%). The same methiodide (by m. p. and mixed m. p.) was formed when the secondary base (VII) (80 mg.) was heated in methanol (2 ml.) with methyl iodide (0·5 ml.) and an excess of aqueous sodium carbonate solution for 4 hr.

N-Benzyl-2 : 2-bis-(3 : 4-dimethoxyphenyl)ethylamine (X).—*N*-Benzyl-2 : 2-dimethoxyethylamine (14·8 g.) was added during 3 hr. to a stirred solution of veratrole (20 g.) in glacial acetic acid (70 ml.) and concentrated sulphuric acid (70 ml.). Stirring was continued for a further 2 hr. and the mixture was then poured on ice (250 g.). The resultant solution was extracted with ether (2 × 250 ml.), and the aqueous layer was basified and extracted with ethyl acetate. Evaporation of the dried organic extracts left a gum which was heated at 100°/0·1 mm. for 5 hr. to remove volatile bases. The resinous product (11·7 g.) in ethanol (200 ml.) was treated with picric acid (11 g.), a solid being precipitated. The solid was extracted with hot acetone and the sparingly soluble picrate (1·27 g.), m. p. 223—224°, was reserved. Concentration of the acetone extract yielded crystals and the same material was obtained when the original ethanolic mother-liquor was evaporated to dryness and the residue dissolved in hot acetone. The two crops were combined and recrystallised from acetone, to give the *picrate* (3·15 g.), m. p. 175·5—176·5°, of the ethylamine (X) (Found: C, 58·9; H, 5·2%; equiv., 644. $C_{31}H_{32}O_{11}N_4$ requires C, 58·5; H, 5·1%; equiv., 636).

9 : 10-Di(benzylaminomethyl)-9 : 10-dihydro-2 : 3 : 6 : 7-tetramethoxyanthracene (XI).—The above picrate, m. p. 223—224°, sparingly soluble in acetone, was recrystallised thrice from acetone, to give the *picrate* of the dihydroanthracene (XI). This separated as prisms, needles, or plates on different occasions, the m. p. of all forms being 225—226° (decomp.) (Found: C, 55·5; H, 4·4. $C_{46}H_{44}O_{18}N_8$ requires C, 55·4; H, 4·4%). The *base* recovered from the picrate, crystallised from ethanol and initially had m. p. 156—158°, but this changed to a gradual softening from 130° to 220° (Found, on freshly prepared material: C, 75·1; H, 7·1%; equiv., 260. $C_{34}H_{36}O_4N_2$ requires C, 75·8; H, 7·1%; equiv., 269). $\lambda_{max.}$ were at 266, 287, 350, and 369 mμ (log ε 3·91, 3·97, 2·69, 2·68 respectively) in EtOH.

2-Benzyl-4-(3 : 4-dimethoxyphenyl)-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxyisoquinoline (XIII) *and its Methiodide.*—The base (X) (0·71 g.) was heated with formic acid and formaldehyde as in the preparation of the *iso*quinoline (VI) above, to give the base (XIII) as a pale yellow gum (0·7 g.). This was dissolved in ether (15 ml.) and methyl iodide (4·5 ml.) and kept for 5 days. The precipitated solid (0·8 g.) crystallised from methanol, to give the *methiodide* of the base (XIII) as colourless needles (0·62 g.), m. p. 228—229° (Found: C, 57·6; H, 5·7; N, 2·5. $C_{27}H_{32}O_4NI$ requires C, 57·7; H, 5·7; N, 2·5%).

1-[2-(N-Benzyl-N-methylaminomethyl)-4 : 5-dimethoxyphenyl]-1-(3 : 4-dimethoxyphenyl)-ethylene (XIV).—The foregoing methiodide (0·266 g.) was degraded as in the two earlier Hofmann degradations, to give the *ethylene* (XIV) as a clear gum (0·187 g.) (Found: equiv., 455. $C_{27}H_{31}O_4N$ requires equiv., 433), $\lambda_{min.}$ 255, $\lambda_{max.}$ 265, $\lambda_{infl.}$ 290 mμ (log ε 4·16, 4·17, 4·04 respectively) in EtOH.

Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a Maintenance Award to R. B. and to Imperial Chemical Industries Limited for gifts of chemicals.

THE UNIVERSITY, BRISTOL. [*Received, June 23rd*, 1958].

XUM

881. *Infrared Spectra, Structure, and Hydrogen-bonding in Ammonium Salts.*

By T. C. Waddington.

Infrared spectra of a series of ammonium salts of monobasic acids have been examined. The spectra of the salts NH_4N_3, NH_4HF_2, NH_4NCO, NH_4NCS, NH_4NO_2, NH_4NO_3 show a combination frequency, $\nu_4 + \nu_6$, involving a torsional mode, and a multiplicity of lines at 3000 cm.$^{-1}$; all these salts have structures differing from those of the potassium and rubidium salts. It is concluded that in these salts the ammonium ion is locked in position in the crystal lattice by hydrogen bonding. No combination frequency, $\nu_4 + \nu_6$, or multiplicity of lines is found in NH_4ClO_4, NH_4BF_4, $NH_4B(C_6H_5)_4$, or NH_4PF_6 and these salts are isomorphous with the corresponding potassium and rubidium salts. It is concluded that in these salts the NH_4^+ ion is free to rotate. In NH_4SO_3F and $NH_4SO_3{\cdot}CH_3$, though a multiplicity of lines at 3000 cm.$^{-1}$ is found, no combination frequency of the torsional mode is detectable and the salts are isomorphous with the potassium and rubidium salts.

Various criteria have been used to determine whether the ammonium ion in an ammonium salt is freely rotating. They are: (1) The distortion of the crystal structure of the ammonium salt from that of the potassium and rubidium salts; (2) the line-width of the proton signal from the ammonium ion in the nuclear magnetic resonance spectrum; (3) specific-heat measurements on the salt; and (4) the infrared spectrum of the salt. Probably none of the criteria is sufficient to establish definitely the presence of free rotation and since in (2) and (3) particularly the experiments are difficult, evidence is only available from all four methods in the ammonium halides, in which the behaviour of the ammonium ion has been clearly established.

However the combination of *X*-ray evidence and infrared spectra can give much information about the behaviour of the ammonium ion in a crystal; we therefore investigated the infrared spectra of a series of ammonium salts of monobasic anions and, where it was unknown, tried to establish the isomorphism of the ammonium and potassium salts.

The ammonium ion has two fundamental frequencies active in the infrared region. They are ν_3, which corresponds to N–H stretching and ν_4, which is a deformation frequency of the ammonium ion. Both are triply degenerate in the freely rotating ion but this degeneracy will disappear if the ammonium ion is not rotating in the lattice, owing to the interaction of the symmetry of the site with that of the ion.

Apart from the thorough and extensive work of Wagner and Hornig [1] and Plumb and Hornig [2] on the infrared spectra of the ammonium halides, that of Dows, Whittle, and Pimentl [3] on ammonium azide and that of Cote and Thompson [4] on ammonium borofluoride, little systematic work has been done on the infrared spectra of the crystalline ammonium salts. Miller and Wilkins [5] have examined the spectra of a number of ammonium salts but theirs was mainly an analytical investigation and no attempt at a detailed assignment was made. Keller and Halford [6] have investigated the spectrum of ammonium nitrate but unfortunately their data are at variance with those of Miller and Wilkins.

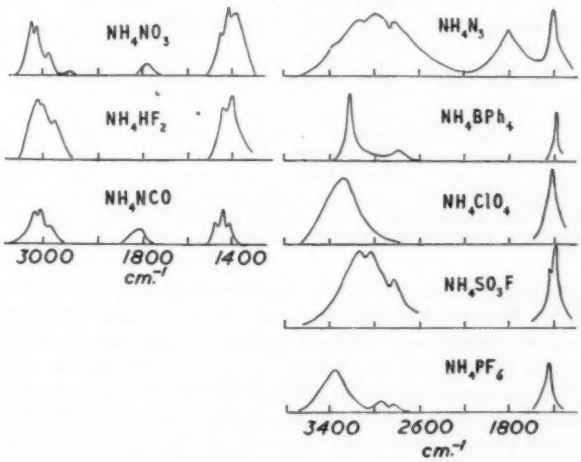
[1] Wagner and Hornig, *J. Chem. Phys.*, 1950, **18**, 296, 305.
[2] Plumb and Hornig, *J. Chem. Phys.*, 1953, **21**, 366, 947.
[3] Dows, Whittle, and Pimentl, *J. Chem. Phys.*, 1955, **23**, 1258.
[4] Cote and Thompson, *Proc. Roy. Soc.*, 1952, *A*, **210**, 217.
[5] Miller and Wilkins, *Ind. Eng. Chem. Anal.*, 1952, **24**, 1253.
[6] Keller and Halford, *J. Chem. Phys.*, 1949, **17**, 26.

XUM

Experimental

Materials.—Ammonium azide was made by passing dry ammonia gas into an ethereal solution of hydrazoic acid. The precipitated ammonium azide was recrystallized from absolute ethyl alcohol and dried *in vacuo*. Ammonium cyanate was prepared by passing dry ammonia gas into a dry ethereal solution of cyanic acid, obtained by warming cyanuric acid in a stream of dry nitrogen and passing the gas through dry ether at −17°. Ammonium hydrogen difluoride was made by adding a slight excess of hydrofluoric acid to aqueous ammonia; the solution was evaporated to dryness in a platinum dish and heated on a water-bath for several hours. Ammonium thiocyanate and nitrate were obtained by recrystallizing the "AnalaR" salt from water. Ammonium nitrite was prepared by treating aqueous barium nitrite with the stoicheiometric quantity of aqueous ammonium sulphate, filtering, and freeze-drying the filtrate. Ammonium borofluoride was obtained as the "AnalaR" salt. Ammonium perchlorate was made by adding excess of aqueous ammonia to aqueous perchloric acid. Ammonium tetraphenylborate was precipitated by treating a filtered aqueous solution of the sodium salt with ammonium chloride. The precipitated salt was recrystallized from acetone. Ammonium fluorosulphate was prepared by treating aqueous fluorosulphonic acid with aqueous ammonia and evaporation. Ammonium methanesulphonate was made in the same manner. Ammonium hexafluorophosphate was kindly provided by Dr. W. G. Palmer.

Apparatus and Methods.—The infrared spectra were measured with a Perkin-Elmer 21 double-beam continuously recording infrared spectrophotometer. Most spectra were recorded



both with rock-salt and with fluorite optics. All solids were finely powdered and mulled with Nujol and with hexachlorobutadiene. In one or two cases a small amount of the powdered solid was mixed with powdered potassium bromide and pressed into a disc.

Results.—The observed frequencies are recorded in Table 1. Since the spectra were taken at room temperature in mulls, only the fairly strong bands were observable and all the features recorded by Hornig and his co-workers for the ammonium halides were not observed. The comparable bands found by Wagner and Hornig and Plumb and Hornig for NH_4Cl, NH_4Br, and NH_4F are also listed. The assignments were made largely on a basis of comparison with Hornig and his co-workers' results. The frequencies ν_4 and ν_3 are both infrared-active, and strong bands corresponding to these modes are found at about 1400 and 3200 cm.$^{-1}$. The first harmonic of ν_4, *i.e.*, $2\nu_4$, is found at around 2800 cm.$^{-1}$ in most of the spectra but its strength varies considerably; the band is very weak in some spectra and much stronger in others. An additional band at 3000—3100 cm.$^{-1}$ is found in some of the spectra. Also in some spectra a band of moderate strength is found in the region 1600—2000 cm.$^{-1}$. This band, in the case of the ammonium and deuteroammonium halides, has been shown by Hornig and his

co-workers, to arise from the interaction of ν_4 with the torsional oscillation ν_6 of the ammonium on its lattice site. Some examples of the shapes of the NH_4^+ bands in the spectra found are shown in the Figure. Only the spectra of the ammonium ions are shown; the spectra of the anions were eliminated by considering the bands common to the potassium and the ammonium salts.

Discussion

Table 1 shows that the variation in the values of the infrared-active fundamentals of the ammonium ion from salt to salt is quite considerable; thus the value of ν_4 ranges from 1484 to 1390 cm.$^{-1}$ and of ν_3 from 3332 to 3100 cm.$^{-1}$. Hydrogen bonding should lengthen the N–H bond and thus shift ν_3 to a lower frequency; it should also raise the value of ν_4. In agreement with this, ammonium fluoride, which might reasonably be expected to be the

Table 1. *Infrared frequencies (cm.$^{-1}$) of the ammonium ion in its monobasic salts.*

Salt	Assignment				
	ν_4	$\nu_4 + \nu_6$	$2\nu_4$	$\nu_2 + \nu_4$	ν_3
NH_4Br	1401 (1429)	1712	2833	3031	3137
NH_4Cl	1403 (1445)	1762	2870	3044	3138
NH_4F	1484 (1503)	2007	2830	3024	3100
NH_4N_3	1414	1810	2830	3000	3140
NH_4NCO	1408 1443 1475	1825	2840	3040	3140
NH_4HF_2	1406 (1445)	*	2875	3050	3140
NH_4NCS	1404 (1435)	1670	2810	3040	3160
NH_4NO_2	1390 (1405)	1753	2785	3010	3150
NH_4NO_3	1420 (1455)	1765	2860	3100	3160
NH_4ClO_4	1425	—	2850	—	3290
NH_4BF_4	1431	—	—	—	3332
NH_4BPh_4	1396	—	2770	—	3222
NH_4PF_6	1433	—	2920	—	3330
NH_4SO_3F	1405 (1448)	—	2830	3500	3150
$NH_4SO_3{\cdot}CH_3$	1414 (1446)	—	2820	2035	3130

* A broad, strong HF_2 band is found in the region 1500—1800 cm.$^{-1}$ with overtones in the region 1800—2000 cm.$^{-1}$ so that failure to identify a $\nu_4 + \nu_6$ for NH_4^+ is not regarded as significant.
( ) a weak side band occurring as a shoulder.

most heavily hydrogen-bonded salt, has the lowest value for ν_3 (3100 cm.$^{-1}$) and the highest for ν_4 (1484 cm.$^{-1}$). However the other ammonium salts do not fit closely into this simple pattern. Fortunately certain correlations do appear to exist and these are discussed below.

There appears to be a strong correlation between the occurrence of the combinational mode $\nu_4 + \nu_6$ and the occurrence of structural differences between the ammonium salts and the corresponding rubidium and potassium salts. Also, in the few cases where nuclear magnetic resonance studies have been undertaken, the salts in which this technique indicates that the NH_4^+ ion is not rotating, NH_4Br, NH_4Cl,[7] and NH_4F,[8] the mode $\nu_4 + \nu_6$ occurs in the infrared region. In the one salt in which nuclear magnetic resonance indicates that the ion NH_4^+ is rotating, NH_4BF_4,[9] no band corresponding to $\nu_4 + \nu_6$ can be found in the infrared. All the ammonium salts in which $\nu_4 + \nu_6$ does not occur are isomorphous with the corresponding potassium and rubidium salts. The results are summarized in Table 2.

It seems reasonable to ascribe the apparent lack of free rotation and the distortion of the crystal structure to hydrogen bonding. It is noteworthy that the frequency ν_6 is highest for the fluoride and lowest for the bromide and thiocyanate with the values for the azide, cyanate, and nitrate intermediate. Such an order would be expected from an *a priori* consideration of the abilities of the atoms concerned to form hydrogen bonds.

Both the frequencies ν_4 and ν_3 are triply degenerate in the freely rotating ammonium

[7] Gutowsky, Pake, and Bersohn, *J. Chem. Phys.*, 1954, **22**, 643.
[8] Drain, *Discuss. Faraday Soc.*, 1955, **19**, 200.
[9] Richards, *Trans. Faraday Soc.*, 1955, **51**, 468.

XUM

ion. However when the ion is locked in position in the crystal lattice the degeneracy is removed and a splitting is expected. The ν_4 band would be expected to produce a triplet with one *A* component and two *B* components. Such a splitting has indeed been observed at low temperatures by Hornig and Wagner for ammonium halides and by Dows, Whittle, and Pimentl for ammonium azide. However at room temperature the bands are considerably

TABLE 2.

Salt	Torsional oscillation ν_6 (cm.$^{-1}$)	Relation between structure.* NH_4^+ salt	K^+ and Rb^+ salts	NMR data
NH_4F	523	Wurtzite	NaCl	Not rotating
NH_4Cl	359	CsCl	NaCl	Not rotating
NH_4Br	311	CsCl	NaCl	Not rotating
NH_4I	None	NaCl	NaCl	Rotating
NH_4N_3	396	Orthorhombic	Tetragonal	—
NH_4CNO	417	Tetragonal [a]	Tetragonal [a]	—
NH_4HF_2	—	Orthorhombic	Tetragonal [b]	—
NH_4CNS	266	Not isomorphous [b, c]		—
NH_4NO_2	363	Not isomorphous [b, c]		—
NH_4NO_3	345	Not isomorphous		—
NH_4ClO_4	None	Isomorphous		—
NH_4BF_4	None	,,		Rotating
NH_4BPh_4	None	,, [c]		—
NH_4PF_6	None	,,		—
NH_4SO_3F	None	,,		—
$NH_4SO_3CH_3$	None	No data		—

* All crystallographic data unless otherwise stated are taken from Landolt–Börnstein, Auflage 6, Band 1, Teil Kristalle 4.

[a] Waddington, unpublished results. [b] T. Davies and L. A. K. Stavely, *Trans. Farad. Soc.*, 1957, **53**, 19. [c] D. W. A. Sharp, personal Communication.

broader and it is not always possible to resolve them. Thus the bands observed at 1441, 1428, and 1420 cm.$^{-1}$ for ammonium azide at 69° K appear as one band at 1415 cm.$^{-1}$ at room temperature. However in several of the ammonium salts even at room temperature it is possible to resolve a weak extra band as a shoulder on the high-frequency side of the principal 1400 cm.$^{-1}$ band. All ammonium salts in which it is possible to do this also show splitting of the 3000 cm.$^{-1}$ band.

The splitting of ν_3 in a fixed ammonium ion should be qualitatively similar to that of ν_4 but since the stretching frequency is much more sensitive to hydrogen bonding than ν_4 the splitting should be quantitatively much larger. Unfortunately the interpretation of these features is complicated by the presence of an overtone in the region 2800 cm.$^{-1}$ ($2\nu_4$) and a combination band in the region 3000—3100 cm.$^{-1}$ ($\nu_4 + \nu_2$). The intensity of the observed overtone band, $2\nu_4$, in the salts in which hydrogen bonding is inferred when compared with the intensity of the same band in NH_4PF_6 or NH_4ClO_4 suggests that this band is not caused solely by the overtone, $2\nu_4$, in the hydrogen-bonded salt. The combination $\nu_2 + \nu_4$ does not appear in the spectrum of NH_4BF_4, NH_4PF_6, NH_4ClO_4, or $NH_4B(C_6H_5)_4$. This suggests that, only when ν_3 is lowered in value and split by hydrogen bonding, can the line $\nu_2 + \nu_4$ interact by Fermi resonance and so gain sufficient intensity to be observed. Also under these conditions the line $2\nu_4$ appears to be able to borrow intensity from the main band.

Though the lowest value for ν_3 and the highest for ν_4 is observed in ammonium fluoride, the values in the other salts do not vary in a simple way. Thus the values of ν_4 for NH_4ClO_4, NH_4BF_4, and NH_4PF_6 are higher than for the salts like NH_3N_3, but that for $NH_4B(C_6H_5)_4$ is lower. Apart from that for NH_4F, the values all lie within a spread of 40 cm.$^{-1}$. The values of ν_3 for NH_4ClO_4, NH_4BF_4, NH_4PF_6, and $NH_4B(C_6H_5)_4$ are all higher than for the salts which have been classed as hydrogen bonded but there is a considerable spread in their values, from 3332 for NH_4BF_4 to 3220 for $NH_4B(C_6H_5)_4$.

X-Ray studies have shown that the salt NH_4SO_3F is isomorphous with KSO_3F and $RbSO_3F$ and indeed with NH_4ClO_4. The absence of a combination mode $\nu_4 + \nu_6$ suggests

strongly that the ammonium ion is not completely locked in position in the lattice. However, a complex structure is found in the 3000 cm.$^{-1}$ region of the infrared spectrum of this salt which is quite unlike that of NH_4ClO_4. Of course the local environment of the ammonium ion must be much less symmetrical than that in NH_4ClO_4 and it is quite possible that this asymmetry is sufficiently strong to remove the degeneracy of the ν_3 mode. Perhaps the same type of behaviour is found in the ammonium ion here as exists in ammonium iodide at room temperature where the ion is hydrogen-bonded to an iodide ion along one bond and is free to rotate about this bond. Possibly a similar position exists in $NH_4SO_3{\cdot}CH_3$ whose infrared spectrum is very similar to that of the fluorosulphate.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, June 24th*, 1958.]

---

882. *Isolation and Structure of Ribitol Phosphate Derivatives (Teichoic Acids) from Bacterial Cell Walls.*

By J. J. ARMSTRONG, J. BADDILEY, J. G. BUCHANAN, B. CARSS, and G. R. GREENBERG.

The cell walls of three Gram-positive bacteria have been shown to contain, as a major component, polymers of ribitol phosphate, called teichoic acids. In addition to ribitol phosphate, the teichoic acids from *Lactobacillus arabinosus* and *Bacillus subtilis* contain α-glucosyl residues joined to ribitol, and *O*-alanyl groups probably linked to glucose. In the teichoic acid from *Staphylococcus aureus* H, an *N*-acylglucosaminyl residue is present in the place of glucose. Trichloroacetic acid extracts of defatted whole cells of *L. arabinosus* and *B. subtilis* contain, in addition to teichoic acids, a polymer of glycerophosphate. The location of the latter within the cells has not been determined.

The accumulation of the nucleotide cytidine diphosphate ribitol by *S. aureus* under conditions favouring accumulation of uridine diphosphate derivatives suggests that the cytidine compound is involved in the biosynthesis of teichoic acids.

A preliminary announcement of some of these results has been made.*

THE two nucleotides, cytidine diphosphate glycerol (CDP-glycerol) and cytidine diphosphate ribitol (CDP-ribitol), were first isolated from *Lactobacillus arabinosus* [1] but are now believed to be more widely distributed in bacteria. CDP-glycerol, whose structure has recently been confirmed by synthesis,[2] contains an L-α-glycerophosphate residue,[3] whereas CDP-ribitol contains a D-ribitol 5-phosphate residue.[4,5] Although the discovery of these nucleotides gave no information about their biological function, it was probable from analogous cases that they would be concerned in the metabolism of glycerophosphate and ribitol phosphate.

Glycerophosphate and its derivatives occur widely in living cells, and it has been suggested already that CDP-glycerol may participate in the biosynthesis of phospholipids [3] and related compounds.[6] It is noteworthy, however, that no experimental evidence has been advanced in support of these suggestions, and even the presence of the nucleotide has not been demonstrated in the biological systems under consideration. The function of CDP-ribitol was even more obscure than that of the glycerol compound, as ribitol

* Armstrong, Baddiley, Buchanan, and Carss, *Nature*, 1958, **181**, 1692.

[1] Baddiley and Mathias, *J.*, 1954, 2723; Baddiley, Buchanan, Carss, Mathias, and Sanderson, *Biochem. J.*, 1956, **64**, 599.
[2] Baddiley, Buchanan, and Sanderson, *J.*, 1958, 3107.
[3] Baddiley, Buchanan, Mathias, and Sanderson, *J.*, 1956, 4186.
[4] Baddiley, Buchanan, Carss, and Mathias, *J.*, 1956, 4583.
[5] Baddiley, Buchanan, and Carss, *J.*, 1957, 1869.
[6] Benson and Maruo, *Biochim. Biophys. Acta*, 1958, **27**, 189.

XUM

phosphate had not been detected hitherto in Nature, and even the free polyol has only been isolated from a few species of plants.

Both CDP-glycerol and CDP-ribitol clearly belong to the group of nucleotide coenzymes, exemplified by uridine diphosphate glucose, in which a phosphoric ester substrate becomes an integral part of the coenzyme. One important function of such coenzymes is in the biosynthesis of macromolecules. Examples of this have been provided recently in the enzymic formation of cellulose [7] and glycogen,[8] where uridine diphosphate glucose participates in the transfer of glucose units, and in chitin synthesis [9] where uridine diphosphate acetylglucosamine serves a similar purpose. Consequently, it was possible that a large-molecular compound containing glycerophosphate or ribitol phosphate residues might occur in *L. arabinosus* and other bacteria.

Freshly grown *L. arabinosus* 17-5 was de-fatted with acetone and extracted with dilute trichloroacetic acid at 0°. Addition of an equal volume of alcohol to the extract, followed by storage at 0°, precipitated a phosphoric ester. The ester was purified further by extraction of the solid with water, followed by precipitation with alcohol, yielding material which was free from ribonucleic acid and gave a clear solution in water.* Evidence described below suggests that this material is not homogeneous, and consequently discussion of the molecular weight of such preparations is of limited value. We believe, however, that the method of isolation, the intractable nature of the material on paper chromatography and electrophoresis, and its very slow rate of dialysis through Cellophane membranes suggest that the molecular weight of the material is not small.

Later work also indicates that a major component is a polymer of ribitol phosphate which bears both glucose and alanine residues and is thus a member of a new group of natural polymers. Before discussing the structure of these remarkable substances some consideration of their biochemical and cytological significance is desirable.

Park and Johnson [10] have demonstrated the accumulation of three nucleotides in *Staphylococcus aureus* during treatment with penicillin: one is uridine diphosphate acetylmuramic acid,[11,12] and the others are derivatives of this bearing either an alanine residue or a small peptide composed of lysine, glutamic acid, and alanine. A connection between the nucleotides and the cell wall followed, since muramic acid is a characteristic component of many bacterial cell walls.[13] Alanine, lysine, and glutamic acid are, moreover, usually found among the relatively small number of amino-acids released by hydrolysis of cell walls.[14,15] It is known that penicillin seriously affects the walls of bacteria during the earlier stages of its action. This is consistent with the observation that the accumulation of the uridine derivatives is also an early effect of penicillin's action.[12,16] It is likely that the nucleotides are involved in the transfer of muramic acid and its peptides into the macromolecular structure of the wall. Penicillin, in interfering with the normal cell-wall structure, presumably causes the accumulation of some of the precursors.

It seemed possible that a similarity in relationship might exist between the uridine derivatives and the muramic acid-peptide residues in cell walls on the one hand, and CDP-ribitol and the ribitol phosphate polymer on the other. Techniques are now available for the isolation of bacterial cell walls uncontaminated by cellular contents.[17] Walls of

* A preliminary account of the isolation of this substance has been published (Baddiley, Buchanan, and Greenberg, *Biochem. J.*, 1957, **66**, 51P).

[7] Glaser, *Biochim. Biophys. Acta*, 1957, **25**, 436.
[8] Leloir and Cardini, *J. Amer. Chem. Soc.*, 1957, **79**, 6340.
[9] Glaser and Brown, *Biochim. Biophys. Acta*, 1957, **23**, 449; *J. Biol. Chem.*, 1957, **228**, 729.
[10] Park and Johnson, *J. Biol. Chem.*, 1949, **179**, 585.
[11] Park, *ibid.*, 1952, **194**, 877, 885.
[12] Park and Strominger, *Science*, 1957, **125**, 99.
[13] Strange, *Biochem. J.*, 1956, **64**, 23P; cf. Work, *Nature*, 1957, **179**, 841.
[14] Salton, *Biochim. Biophys. Acta*, 1953, **10**, 512.
[15] Cummins and Harris, *J. Gen. Microbiol.*, 1956, **14**, 583.
[16] Strominger, *J. Biol. Chem.*, 1957, **224**, 509.
[17] Salton and Horne, *Biochim. Biophys. Acta*, 1951, **7**, 177.

L. arabinosus prepared in this way were kindly supplied by Dr. M. R. J. Salton. Hydrolysis of a sample with hot acid, followed by paper chromatography, showed the presence in the hydrolysate of ribitol phosphates, inorganic phosphate, and 1 : 4-anhydroribitol, together with other compounds expected from the hydrolysis of a polymer of ribitol phosphate (see below).* Moreover, direct extraction of the cell walls with cold trichloroacetic acid, followed by addition of alcohol to the extract, yielded a compound apparently identical with the ribitol-containing component of the material obtained earlier from whole cells. Closely related compounds of very similar composition are present in the cell walls of *S. aureus* H (kindly provided by Dr. J. T. Park) and *Bacillus subtilis*. We have been unable to detect derivatives of ribitol phosphate in the walls of *Micrococcus lysodeikticus* and *Escherichia coli*. The general name " teichoic acid " (Greek τεῖχος = wall) is suggested for these polymers of ribitol phosphate with or without other substituents. Although the presence of teichoic acid in other bacteria has not yet been examined, it is likely that it will be found fairly widely. Its function in cell walls is not known, but its absence from the spore walls of *B. subtilis* suggests that it may be concerned in the metabolism of actively growing cells.

By visual estimation from paper chromatograms, the amount of inorganic phosphate liberated on acid hydrolysis of cell walls corresponds on a molar basis to the amount of 1 : 4-anhydroribitol formed. These two materials are known to be the main products of decomposition of ribitol phosphates under strongly acidic conditions.[4,18,19] The only organic phosphates detected in hydrolysates of walls are those expected from teichoic acid; consequently, from a determination of the phosphorus content of the walls, their teichoic acid content can be calculated. In this way it was found that 40—60% of the walls of *S. aureus* and *B. subtilis* consists of teichoic acid. The amount present in *L. arabinosus* may even exceed 60%. It follows that this is a major wall component in all these bacteria.

Although teichoic acid is freely soluble in water, the washing techniques employed in the isolation of walls had failed to remove it. On the other hand, about one-third of the total amount present in the walls examined so far is readily extracted by cold trichloroacetic acid. Apparently the extractable fraction is held in the wall by electrovalent linkage. It is not known whether the remainder is chemically bound to other wall components.

It is highly probable that CDP-ribitol is concerned in the successive condensation of ribitol phosphate residues during the biosynthesis of teichoic acid. Although the details of the enzymic synthesis have not been examined, a close similarity in function between CDP-ribitol and Park's nucleotides is apparent. Moreover, a cytidine derivative accumulates in *S. aureus* during growth in the presence of chloramphenicol (personal communiccation from Dr. J. T. Park). We have identified this nucleotide as CDP-ribitol by comparison with authentic material on paper chromatograms, and by acid hydrolysis to cytidine-5′ phosphate, ribitol phosphates, and their decomposition products. Similarly, when *S. aureus* is grown in the presence of Crystal Violet a cytidine derivative accumulates. A sample of this nucleotide (kindly provided by Dr. J. L. Strominger) has been identified as CDP-ribitol by Dr. A. R. Sanderson in this laboratory. It seems that penicillin, chloramphenicol, and certain other inhibitors, by interfering either directly or indirectly with cell-wall formation, cause the accumulation of the uridine precursors and in some cases the cytidine precursors.

Acid-hydrolysis of teichoic acid obtained from the walls of *L. arabinosus* yielded the following compounds (see Table 1), all identified by comparison on paper chromatograms with authentic substances: alanine, glucose, ribitol and its isomeric monophosphates, 1 : 4-anhydroribitol, 1 : 4-anhydroribitol 5-phosphate, and inorganic phosphate. No other sugars, amino-acids, polyols, or organic phosphates were detected in the hydrolysate.

* A preliminary account of this observation has been published by Baddiley, Buchanan, and Carss, *Biochim. Biophys. Acta*, 1958, **27**, 220.

[18] Baddiley, Buchanan, and Carss, *J.*, 1957, 4058.
[19] *Idem, ibid.*, p. 4138.

XUM

Confirmation of the identity of the organic phosphates was obtained by enzymic hydrolysis to the respective polyols and inorganic phosphate. 1 : 4-Anhydroribitol 5-phosphate, which has not been described previously, gave the slow-developing blue colour reaction, typical of cyclic glycols, on paper chromatograms sprayed with the periodate–Schiff reagents. It yielded anhydroribitol on enzymic dephosphorylation, and was indistinguishable from a synthetic sample prepared in these laboratories by Mr. R. Cowling. When teichoic acid from whole bacterial cells was hydrolysed in acid, the products included all

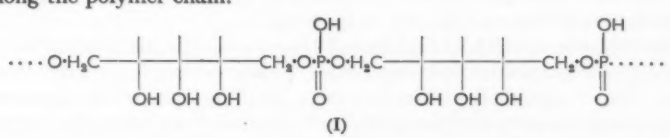
TABLE 1. *Products of acid hydrolysis of teichoic acid from different bacteria.*

	L. arabinosus	*B. subtilis*	*S. aureus*
Alanine	+	+	+
Glucose	+	+	—
Glucosamine	—	—	+
Inorganic phosphate	+	+	+
1 : 4-Anhydroribitol	+	+	+
1 : 4-Anhydroribitol 5-phosphate	+	+	+
Ribitol phosphates	+	+	+
Ribitol	+	+	+
Ribitol glucosaminide	—	—	+

those described for the wall material, but glycerol and its phosphates were also detected. The absence of glycerol derivatives from cell walls, and the variable amounts present in different teichoic acid preparations from whole cells of *L. arabinosus* and *B. subtilis*, suggest that these products do not represent residues in teichoic acid, but are probably derived from a glycerophosphate polymer which accompanies the acid when obtained from whole cells. The possible significance of this glycerophosphate polymer is discussed on p. 4350.

The formation of ribitol, 1 : 4-anhydroribitol, and their respective phosphates on acid hydrolysis is consistent with the presence in teichoic acid of a polymeric structure, *e.g.*, (I) or its isomers, in which ribitol residues are joined together through phosphodiester linkages. At pH values lower than 4, ribitol monophosphates decompose largely to 1 : 4-anhydroribitol and inorganic phosphate; at the same time equilibration between the isomeric ribitol monophosphates occurs through acid-catalysed migration of the phosphate.[18] Although traces of 1 : 4-anhydroribitol 5-phosphate are formed at these low pH values, no ribitol is liberated. Possible mechanisms for these reactions have been discussed previously.

In a polymer of ribitol phosphate, *e.g.*, (I), acid-catalysed hydrolysis might occur in a more or less random manner. Consequently, the primary hydrolysis products would include ribitol and its mono- and di-phosphate. Ribitol, once formed, would be relatively stable under the conditions of our experiments, but the monophosphates would be largely converted into 1 : 4-anhydroribitol and a trace of its 5-phosphate. Similarly, diphosphates of ribitol would be converted into 1 : 4-anhydroribitol 5-phosphate. The amount of 1 : 4-anhydroribitol 5-phosphate formed by hydrolysis of teichoic acid (estimated visually from paper chromatograms) is considerably greater than would be expected from hydrolysis of ribitol phosphate itself. This, and the presence of free ribitol in hydrolysates, indicates that teichoic acid must contain a chain of ribitol residues linked through phosphodiester groups. It also follows that fission of the secondary phosphate groups can occur in either direction along the polymer chain.



(I)

The hydrolysis of phosphomonoesters at pH 4 takes a different course from that which occurs at low pH values.[20] Hydrolysis of the monoanion occurs smoothly and readily

[18] Desjobert, *Compt. rend.*, 1947, **224**, 575; *Bull. Soc. chim. France*, 1947, **14**, 809; Butcher and Westheimer, *J. Amer. Chem. Soc.*, 1955, **77**, 2420.

with glycerophosphates,[21] ribitol phosphates,[18] and nucleotides [22] to give the respective hydroxy-compounds and inorganic phosphate. Under conditions which convert ribitol phosphates quantitatively into ribitol and inorganic phosphate, the phosphate groups in teichoic acid were almost unaffected. Only a trace of inorganic phosphate was liberated, thus indicating the absence of phosphomonoester groups. Phosphodiesters are relatively stable at pH 4.

Preparations of teichoic acid, whether from whole cells or walls of *L. arabinosus* or *B. subtilis*, yielded alanine and glucose on acid hydrolysis. Further attempts to purify the material by paper chromatography, electrophoresis, or adsorption on charcoal did not alter the relative amounts of these two hydrolysis products, which were present in the ratio 1 : 1. The glucose in the intact compound was non-reducing, readily liberated as glucose by acid hydrolysis, and was unaffected by hot alkali. These properties are consistent with those of a glucoside. The stability of the sugar residues to alkali eliminates the possibility of a linkage between glucose and the remainder of the molecule through a phosphate group. No disaccharides or larger sugar groupings were observed on partial acid hydrolysis of teichoic acid. It is likely then that each glucose unit is joined individually as a glucoside residue to the polymer.

Further information about the nature of the glucoside linkages in teichoic acid comes from its behaviour towards alkali. Although phosphodiesters are normally stable to alkali, they become liable if one or both of the alkyl groups bears a hydroxyl adjacent to the phosphoric ester group. The products of such hydrolyses are usually mixtures of isomeric hydroxyalkyl phosphates.[23] When the acid from *L. arabinosus* was heated with sodium hydroxide solution a mixture of phosphoric esters was obtained. The main components of this mixture were monoesters which, on dephosphorylation with prostate phosphomonoesterase, yielded ribitol derivatives (see Table 2). These were separated into two

TABLE 2. *Products of alkali-hydrolysis, followed by enzymic dephosphorylation, of teichoic acid from different bacteria.*

	L. arabinosus	*B. subtilis*	*S. aureus*
Alanine	+	+	+
Inorganic phosphate	+	+	+
Ribitol monoglucosides	+	+	—
Ribitol diglucoside	+	—	—
Ribitol	+	—	—
Anhydropentitol	+	+	+
Ribitol glucosaminide	—	—	+
Residual phosphoric ester	+	—	—

fractions by paper chromatography in *n*-propyl alcohol–ammonia–water. The faster-moving material gave equimolar amounts of glucose and anhydroribitol on prolonged acid hydrolysis, whereas the slower-moving material gave glucose and anhydroribitol in the molar ratio of 2 : 1. Partial acid hydrolysis of these fractions yielded some ribitol as well as anhydroribitol, and it is concluded that they contain mono- and di-glucosides of ribitol. The faster-moving material was not homogeneous, and at least two, and possibly three, closely related ribitol glucosides were detected. These are presumably isomers in which a glucosyl substituent occupies different positions on the ribitol residue. Further work on the characterisation of these products is in progress.

Alkali-hydrolysates of teichoic acid from *L. arabinosus* contain, in addition to the phosphates of the ribitol glucosides described above, a slower-moving phosphate or mixture of phosphates. This fragment is resistant to both alkali and phosphomonoesterase, but on acid treatment it gives inorganic phosphate, anhydroribitol, and the other products of acid hydrolysis of the ribitol glucoside phosphates. It probably represents a fragment of the

[21] Bailly, *Bull. Soc. chim. France*, 1942, **9**, 340.
[22] Baddiley, Buchanan, and Letters, *J.*, 1958, 1000.
[23] Bailly and Gaumé, *Bull. Soc. chim. France*, 1935, **2**, 354; 1936, **3**, 1396; Baer and Kates, *J. Biol. Chem.*, 1948, **175**, 79; 1950, **185**, 615; Brown and Todd, *J.*, 1952, 52.

XUM

teichoic acid where secondary phosphate groups have withstood the action of alkali. This could occur where substituents (presumably glucose units) occupy hydroxyl groups on the ribitol residues adjacent to the phosphate groups.

Neither teichoic acid nor the ribitol glucosides obtained from it were hydrolysed by a commercial β-glucosidase preparation, and it is likely that the glucoside linkages are all α. The pronounced positive rotation, $[\alpha]_D + 80{\cdot}4°$, of teichoic acid from *L. arabinosus* is consistent with this view, on the assumption that the main contribution to the rotation will be made by the glucose fraction (25%) of the molecule.

Not all the ribitol residues in teichoic acid from *L. arabinosus* bear one or two glucosyl substituents. Alkali-hydrolysates which have been treated with prostate phosphatase contain appreciable amounts of ribitol. This must have arisen from ribitol residues which did not bear glucosyl substituents.

It is interesting that alkali-hydrolysates always contain a small quantity of an anhydropentitol. Although this is indistinguishable from 1 : 4-anhydroribitol on paper chromatography, it has not been fully identified. The same compound is also formed in very small amounts by the prolonged action of alkali on ribitol phosphates. The mechanism of its formation clearly differs from that which operates under acidic conditions.

Teichoic acids from all sources examined so far yield alanine on acid- or alkali-hydrolysis. The strong positive ninhydrin reaction shown by all preparations suggests that the amino-group in the alanine residue is unsubstituted. Moreover, the great instability of these residues towards alkali suggests that they are joined to the polymer in ester linkage through their carboxyl groups. The reaction of teichoic acid with ammonia confirms this view. Even under the mild conditions of paper chromatography in an ammoniacal solvent the alanine residues were removed completely. The products from these residues were identified by paper chromatography as alanine and its amide. Alanine ethyl ester behaved similarly under comparable conditions. Moreover, the polymer readily yields alanine hydroxamic acid on treatment with hydroxylamine. The alanine ester residues must be attached to a hydroxyl group in either the glucose or ribitol residues in the polymer, but evidence for their exact location is not yet available. We believe that this is the first authentic example of the occurrence of an α-amino-ester in Nature.

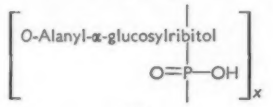
It is of interest that alanine residues bearing free amino-groups have been detected by Brown [24] in cell walls and trichloroacetic acid-extracts of walls. These were described as *N*-terminal groups, presumably of peptide chains. It is probable that most or all of these are alanine ester groups associated with the teichoic acid which would be present in the preparations. Similarly, *O*-acetyl groups have been detected in bacterial walls.[25] These are believed to be associated with sugar residues in the mucopolysaccharide fraction of the walls.[26] It is worth emphasising that the method used in their quantitative determination, *i.e.*, reaction with hydroxylamine followed by addition of a ferric salt, would not normally distinguish between *O*-acetyl and *O*-alanyl groups. This could be misleading in experiments with walls which contain appreciable amounts of teichoic acid.

Preliminary experiments on teichoic acid from *B. subtilis* suggest that the alanine residues are attached directly to the sugar groups. The ribitol residues in this material are destroyed by oxidation with periodate at pH 4·5 during 24 hours. Little or no loss of alanine would occur under these conditions. It follows that an unsubstituted glycol group must be present in each ribitol residue. As the ribitol residues are already substituted in three positions (once by glucose and twice by phosphate), the alanine ester grouping must occur on the sugar residues.

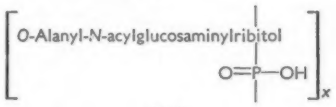
A general structure for teichoic acid, based on the above considerations, is shown in formula (II). This is clearly an over-simplification in the case of the acid from *L. arabinosus*, where some ribitol units have two glucosyl residues, whereas others have none. It is even

[24] Brown, *Biochim. Biophys. Acta*, 1958, **28**, 445.
[25] Abrams, *J. Biol. Chem.*, 1958, **230**, 949.
[26] Brumfitt, Wardlaw, and Park, *Nature*, 1958, **181**, 1783.

possible that the alkali-resistant phosphate obtained from this acid corresponds to ribitol units bearing three glucose residues. On the other hand, teichoic acid from *B. subtilis* is probably more closely represented by formula (II). Alkali hydrolysis, followed by phosphatase treatment, of the acid from this organism gave only one ribitol glucoside, and no ribitol or alkali-resistant phosphates were detected (Table 2).



(II)



(III)

Teichoic acid from *S. aureus* differs from the other two described in this paper in that, although it contains alanine ester groups and gives all the degradation products of ribitol phosphates on acid hydrolysis, it does not contain glucose. In this material *N*-acetylglucosamine takes the place of glucose in a relatively simple polymer (III), similar in composition to that from *B. subtilis*. Acid hydrolysates (Table 1) contained glucosamine (identified by the Elson–Morgan test [27] on paper chromatograms and by the slowly developing ninhydrin colour reaction) and a small amount of a ribitol glucosaminide. The identity of glucosamine was confirmed by eluting the purple area of a paper which had been sprayed with ninhydrin solution containing pyridine, and identifying as arabinose the sugar which was formed.[28] The glucosaminide was the only glucosamine-containing product of alkali hydrolysis and phosphatase treatment of the polymer (Table 2). It gave a typical glycoside reaction with the periodate–Schiff reagents for glycols, and a purple colour with ninhydrin. Unlike the original material, it was fairly stable towards acids. On prolonged acid-hydrolysis the products were glucosamine and anhydroribitol.

Acid-hydrolysis of glucosaminides and their *N*-acetyl derivatives has been studied by Foster, Horton, and Stacey,[29] who noted the stability of glucosaminides and concluded that during acid hydrolysis of their *N*-acetyl derivatives two competing reactions occurred. Fission of the glycosidic linkage in the *N*-acetylglucosaminides proceeds readily, but the gradual hydrolysis of the acetyl group in the glycoside gives rise to some free glucosaminide which resists further hydrolysis. These conclusions are in agreement with our findings on the teichoic acid from *S. aureus*. The relative ease with which glucosamine is liberated by acid-hydrolysis suggests the presence of an *N*-acyl substituent. The formation of a small amount of ribitol glucosaminide under acidic conditions is consistent with this view. Under alkaline conditions the acyl group is presumably lost, giving rise to the glucosaminide which would only be hydrolysed slowly by acids. Although we have not identified the acyl substituent, it is probably an acetyl group, since *N*-acetyl-D-glucosamine occurs widely in Nature.

The structure and significance of the glycerophosphate derivative which accompanies teichoic acid when isolated from whole cells is not clear. The high water-solubility and low alcohol-solubility of this material strongly indicate the absence of long-chain fatty ester groups. On acid hydrolysis it gave glycerol, glycerophosphates, and glycerol diphosphates, all identified by paper chromatography and enzymic dephosphorylation to glycerol and inorganic phosphate. Similarly, alkali hydrolysis gave a mixture of glycerol and its mono- and di-phosphate. It follows that this compound is a polymer of glycerophosphate of unknown molecular weight.

It is highly probable that CDP-glycerol is concerned in the biosynthesis of the glycerophosphate polymer, presumably by successive condensation of glycerophosphate residues. The absence of this polymer from the cell walls examined so far, and the failure of CDP-glycerol to accumulate in inhibition studies with Crystal Violet in *S. aureus*, suggest that

[27] Elson and Morgan, *Biochem. J.*, 1933, **27**, 1824.
[28] Stoffyn and Jeanloz, *Arch. Biochem. Biophys.*, 1954, **52**, 373.
[29] Foster, Horton, and Stacey, *J.*, 1957, 81.

XUM

the glycerol polymer is not involved in the cell wall. Macromolecular material of uncertain composition, containing glycerophosphate residues, has been isolated from bacteria by Mitchell and Moyle.[30] It is possible that this originated from the protoplast membrane, a thin membrane lying just beneath the cell wall.[31] Recent analyses of such membranes from *M. leisodeikticus* indicate that they contain a glycerophosphate polymer.[32] However, this material is thought to contain long-chain fatty ester groups and it is uncertain what relation it bears to our polymer.

Experimental

Isolation of Teichoic Acid from L. arabinosus *Cells.*—*L. arabinosus* 17-5 was grown in bottles (10 l.) without aeration on a hydrolysed casein medium, supplemented with yeast extract and trace elements, as described previously.[1] The cells (65 g. wet) were harvested in a Sharples centrifuge and washed three times with 0·8% sodium chloride solution at 0°. They were successively treated in a Waring blendor (30 sec.) with acetone, alcohol, and ether (15 vol.) at room temperature.

The fat-free cells (24 g.) were treated for 1 min. in the blendor with three portions (100 ml. each) of ice-cold 10% trichloroacetic acid. After centrifugation, the combined supernatant solutions were filtered once through " Supercel " and treated with an equal volume of alcohol at 0°. After 12 hr. the material was isolated by centrifugation, reprecipitated from ice-cold 10% trichloroacetic acid (75 ml.) by addition of an equal volume of alcohol, then washed with acetone and ether. The yield was 56 mg. of a white powder containing a little nucleic acid and a high proportion of polyglycerophosphate (Found: P, 8·2; glucose,[33] 22·3; alanine,[34] 11·9%. This represents a molar ratio of glucose : alanine = 1·0 : 1·1).

The cell debris was treated in the blendor (3 min.) with ice-cold 10% trichloroacetic acid (200 ml.), left overnight at 0°, then treated for a further 1 min. in the blendor. The supernant solution, after centrifugation of debris, was filtered once through " Supercel " and mixed with an equal volume of alcohol. After 24 hr. the precipitate (225 mg.) was collected by centrifugation and washed with acetone and ether. Nucleic acid was removed by trituration with water (10 ml.) for several min., followed by clarification in a centrifuge. After 3 days at 0° a further small precipitate was removed from the solution which was next adjusted to pH 6·5 with dilute ammonia. Acetone (1·5 vol.) was added at 0° and after 24 hr. teichoic acid (28 mg.) was collected as a clear resin which solidified to a glass on drying. It contained a little polyglycerophosphate and no nucleic acid (Found: glucose, 25·4%) and had $[\alpha]_D^{19}$ +80·4° (*c* 2·1 in water).

Isolation of Teichoic Acid from B. subtilis *Cells.*—*B. Subtilis* was grown in bottles (10 l.) with aeration on a peptone (2·0%)–sodium chloride (0·5%) medium. Growth was allowed to take place for 48 hr. at 20—22°. The cells (55 g. wet) were harvested in a Sharples centrifuge and washed with 0·8% sodium chloride solution at 0°. They were successively treated in a Waring blendor (30 sec.) with acetone, alcohol, and ether (15 vol.) at room temperature.

More vigorous conditions were required to remove teichoic acid from *B. subtilis* cells than from *L. arabinosus* cells. Fat-free cells (20 g.), treated (3 × 1 min.) in the blendor with 100 ml. portions of ice-cold 10% trichloroacetic acid as described for *L. arabinosus*, yielded no teichoic acid. The residue from this extraction was treated in the blendor (3 min.) with ice-cold 10% trichloroacetic acid (200 ml.), left overnight at 0°, then treated for a further 1 min. in the blendor. The supernatant solution, after centrifugation of debris, was filtered through " Supercel " and mixed with an equal volume of alcohol. After 24 hr. at 0° the precipitate (291 mg). was collected by centrifugation and washed with acetone and ether. Trituration of the precipitate with water (11·0 ml.) dissolved the teichoic acid, and the nucleic acid was removed by centrifugation. After 3 days at 0° a further small precipitate was removed from the solution which was then adjusted to pH 6·5 with dilute aqueous ammonia. Acetone (2 vol.) was added at 0° and after 48 hr. teichoic acid (63 mg.) was collected as a clear resin which solidified

[30] Mitchell and Moyle, *J. Gen. Microbiol.*, 1951, **5**, 981.
[31] McQuillen, *Biochim. Biophys. Acta*, 1955, **17**, 382; Mitchell and Moyle, *J. Gen. Microbiol.*, 1956, **15**, 512.
[32] McQuillen, personal communication.
[33] Park and Johnson, *J. Biol. Chem.*, 1949, **181**, 149.
[34] Meyer, *Biochem. J.*, 1957, **67**, 333.

XUM

to a glass on drying. It contained a little polyglycerophosphate and faint traces of nucleic acid.

TABLE 3.

	R_F in solvent			IO_4^-–Schiff reaction *	Ninhydrin reaction
	A	B	C		
Glucose	0·61	0·76	0·27	S, W	—
Glucosamine	0·61	0·46	0·21	S, W	+
Glycerol	0·75	—	0·49	R	—
Ribitol	0·65	0·83	0·30	R	—
Anhydroribitol	0·75	0·88	0·47	S	—
Glycerophosphates	0·33	—	—	R	—
Ribitol 1-phosphate	0·30	—	—	R	—
Ribitol 2(and 3)-phosphates	0·33	—	—	R	—
Anhydroribitol 5-phosphate	0·29	—	—	S	—
Inorganic phosphate	0·17	—	—	—	—
" Resistant phosphate "	0·13	—	—	S	—
Ribitol diphosphate	0·12	—	—	S, W	—
Glycerol diphosphate	0·12	—	—	—	—
Alanine	0·63	0·67	0·30	—	+
Alanine amide	0·72	—	—	—	+
Ribitol glucosides	0·55	—	—	R	—
Ribitol diglucoside	0·40	—	—	R	—
Ribitol glucosaminide	0·56	—	—	R	+

* S = slow reaction, R = rapid reaction, W = weak reaction.

Isolation of Teichoic Acid from Bacterial Cell Walls.—50 mg. of a cell-wall preparation (*L. arabinosus* or *S. aureus*) was stirred with 10% trichloroacetic acid (1·5 ml.) overnight at 0°. The cell walls were centrifuged and extracted again with 10% trichloroacetic acid (1 ml.). The combined supernatant solutions were mixed with acetone (2 vol.) and kept at 0° overnight. Teichoic acid was precipitated as a clear resin which solidified to a glass on drying (yield: 5 mg. from *L. arabinosus*; 2·2 mg. from *S. aureus*).

Acid-hydrolysis of Teichoic Acid.—Teichoic acid (1·0 mg.) from the above sources and from *B. subtilis* cells was hydrolysed in 2N-hydrochloric acid in a sealed tube for 3 hr. at 100°. After evaporation the samples were examined by paper chromatography in solvent systems *A*, *B*, and *C* (cf. p. 4354). Products were detected by the molybdate reagent for phosphoric esters,[35] the periodate–Schiff reagents for α-glycols,[36] the aniline phthalate reagent for reducing sugars,[37] the ninhydrin reagent for amino-acids, [38] the Elson–Morgan reagents for amino-sugars,[27] and by inspection in ultraviolet light. Products detected are given in Table 1 and R_F values in Table 3.

Alkali-hydrolysis and Enzymic Dephosphorylation.—Teichoic acid samples (10 mg.) were heated in N-sodium hydroxide solution (50 μl.) for 3 hr. at 100°. Na^+ ions were removed by passing the hydrolysate through a small column of Dowex-50 (NH_4^+ form) resin. Ammonia was evaporated from the eluate, its pH was adjusted to 5·5 with acetic acid, and the volume was adjusted to 0·2 ml. A preparation of prostate phosphatase (0·1 ml.) was added and the solution was kept under toluene at 37° for 24 hr. After suitable adjustment of the volume, the solution was chromatographed as a band in solvent system *A*. The products (polyols, glucosides, or glucosaminides) were detected on " marker strips " by using the above spray reagents. They were isolated for further investigation by elution of the appropriate area of the chromatogram. A summary of these results is given in Table 2 and R_F values in Table 3.

Analysis of Ribitol Glucosides.—The glucoside spots obtained by the above experiment from *L. arabinosus* were eluted from the chromatogram and separately hydrolysed to glucose and anhydroribitol by heating them at 100° with 2N-hydrochloric acid for 24 hr. After removal of solvent the products were chromatographed in solvent system A and strips containing glucose and anhydroribitol were cut out and eluted. Glucose was estimated as before, and anhydroribitol by quantitative periodate oxidation on a microscale.[39] Control solutions for the estimation were made by eluting strips cut from appropriate areas between tracks on the paper.

[35] Hanes and Isherwood, *Nature*, 1949, **164**, 1107.
[36] Buchanan, Dekker, and Long, *J.*, 1950, 3162; Baddiley, Buchanan, Handschumacher, and Prescott, *J.*, 1956, 2818.
[37] Partridge, *Nature*, 1949, **164**, 443.
[38] Consden and Gordon, *ibid.*, 1948, **162**, 180.
[39] Dixon and Lipkin, *Analyt. Chem.*, 1954, **26**, 1092.

The material with the higher R_F value contained glucose and anhydroribitol (originally ribitol) in the ratio of 0·92 : 1·0, and the slower-running material gave a corresponding ratio of 1·84 : 1·0.

Periodate Oxidation of Teichoic Acid.—Teichoic acids from whole cells of *L. arabinosus* and *B. subtilis* were used: 0·5 mg. was dissolved in 1% sodium metaperiodate solution (80 μl.) and kept in the dark for 24 hr. The solution was then treated with sulphur dioxide to destroy excess of periodate, and 12N-hydrochloric acid (15 μl.) was added. After hydrolysis for 24 hr. at 100°, followed by removal of solvent, the products were chromatographed in solvent system *A*. A sample (0·5 mg.) of teichoic acid was treated with ammonia solution (*d* 0·88) for 20 min. at room temperature to remove alanine residues. After removal of ammonia, oxidation and hydrolysis were carried out as above. In a control experiment the oxidation step was omitted. The paper was sprayed with the periodate–Schiff reagents, and the anhydroribitol was estimated visually. Periodate oxidation (with or without pre-treatment with ammonia) of teichoic acid from *L. arabinosus* reduced only slightly the amount of anhydroribitol finally formed, *i.e.*, most of the ribitol residues resist periodate oxidation. However, the same treatment of teichoic acid from *B. subtilis* destroyed nearly all the ribitol residues and only a trace of anhydroribitol was finally formed.

It was shown in a separate experiment that no alanine residues are removed from teichoic acid under the conditions of the periodate oxidation.

Phosphorus Analysis, and Teichoic Acid Content of Bacterial Cell Walls.—The cell wall preparations studied had the following phosphorus content (Allen's method [40]): *L. arabinosus*, 3·4; *B. subtilis*, 4·2; *S. aureus*, 2·9%. Thus *L. arabinosus* wall is calculated to consist of 49—75% teichoic acid, depending on the proportions of ribitol residues possessing one, or two alanylglucosyl residues; *B. subtilis* and *S. aureus* walls contain 61 and 42% of teichoic acid respectively.

Formation of Alanine and Alanine Amide from Teichoic Acid.—Teichoic acid (0·5 mg.) from *L. arabinosus*, *S. aureus*, and *B. subtilis* was dissolved in water (10 μl.) and chromatographed on paper in *n*-butyl alcohol saturated with water. The dried chromatogram was sprayed with the ninhydrin reagent. Teichoic acid remained on the origin and gave a positive reaction. No free alanine was detected. A similar chromatogram was run in the ammoniacal solvent system *A*. The teichoic acid remaining on the origin did not react with ninhydrin and an elongated spot was observed which stretched from the R_F of alanine amide to that of alanine.

Teichoic acid (0·5 mg.) and α-alanine ethyl ester (0·25 mg.) were separately treated with ethyl alcohol–ammonia (*d* 0·88) (1 : 1; 10 μl.) and kept overnight at room temperature. Paper chromatography of the products in solvent system *A* showed that α-alanine ethyl ester had completely decomposed, giving a mixture of alanine and alanine amide, the latter predominating. This behaviour was also observed with teichoic acid.

Action of Hydroxylamine on Teichoic Acid.—Teichoic acid (1·0 mg.) from *L. arabinosus* was allowed to react with hydroxylamine under conditions similar to those described by Kaye and Kent,[41] and the products were examined on paper in *n*-butyl alcohol–acetic acid–water (4 : 1 : 5) (organic layer), and *n*-butyl alcohol saturated with water. Spraying of the chromatograms with a solution of ferric chloride in dilute hydrochloric acid showed a reddish spot indistinguishable in R_F from the hydroxamic acid derivative of alanine, produced from alanine ethyl ester by reaction with hydroxylamine. No acethydroxamic acid was detected in the products of reaction of teichoic acid and hydroxylamine, suggesting the absence of *O*-acetyl groups in the intact polymer.

Confirmation of the Identity of Alanine in Teichoic Acid.—Teichoic acid (3 mg.) from *L. arabinosus* was hydrolysed in a sealed tube with 2N-hydrochloric acid at 100° for 3 hr. After removal of the solvent the products were run as a band in solvent system A. Only one ninhydrin-positive band was detected. It was cut out and eluted, and the products were examined alongside authentic alanine in solvent systems *B*, *C*, and also phenol–water (9 : 1), *n*-butyl alcohol–acetic acid–water (4 : 1 : 5) (organic layer), *n*-butyl alcohol saturated with water, and methanol–water–10N-hydrochloric acid–pyridine (80 : 17·5 : 2·5 : 10). The chromatograms run in the last-named solvent were dipped in a 0·1% solution of ninhydrin in acetone before heating; the others were sprayed with the usual ninhydrin reagent. In every case only alanine was detected.

Paper Chromatography.—Ascending-front chromatography was carried out on Whatman

[40] Allen, *Biochem. J.*, 1940, **34**, 858.
[41] Kaye and Kent, *J.*, 1953, 79.

No. 4 paper which had been washed with 2N-acetic acid, then water. The following solvent systems were used: *A*, *n*-Propyl alcohol–ammonia (*d* 0·88)–water (6 : 3 : 1).[38] *B*, *iso*Propyl alcohol–12N-hydrochloric acid–water (65 : 17 : 18).[42] *C*, *n*-Butyl alcohol–ethyl alcohol–water–ammonia (*d* 0·88) (organic layer) (40 : 10 : 49 : 1).[29]

We are grateful to Drs. K. McQuillen, J. T. Park, and M. R. J. Salton for helpful discussions and samples, and the Rockefeller Foundation and the Nuffield Foundation for grants. This work was carried out during the tenure of a D.S.I.R. Research Studentship (J. J. A.) and a National Science Foundation Senior Research Fellowship (G. R. G.).

KING'S COLLEGE, UNIVERSITY OF DURHAM,
NEWCASTLE UPON TYNE. [*Received, July 24th*, 1958.]

[42] Smith and Wyatt, *Biochem. J.*, 1951, **49**, 144.

---

883. *The Rearrangement of Aromatic* N-*Nitroamines. Part II.* Isotopic Test for Intramolecular Character in the Nitro-transfers from Side-chain to* ortho- *and* para-*Positions.*

By S. BROWNSTEIN, C. A. BUNTON, and E. D. HUGHES.

It was known from previous work that the main part of the rearrangement of *N*-nitroaniline in aqueous sulphuric acid, which produces 93% of *o*-nitroaniline and 7% of *p*-nitroaniline, is intramolecular. However, the previous work was not quantitative enough to exclude the possibility that the *para*-product and perhaps a little of the *ortho*-isomer might arise from a concurrent acidolysis of the *N*-nitro-group and subsequent *C*-nitration by the nitric acid formed. This possibility is now excluded by showing that no trace of a nitrogen-isotopic label contained in nitric acid introduced into the medium used for the rearrangement appears in either the *o*- or the *p*-nitroaniline. Both products are therefore formed exclusively by intramolecular mechanisms, concerning which a suggestion is made.

BAMBERGER showed that *N*-nitroaniline and similar nitro-amines undergo rearrangement under the influence of acids to form *C*-nitroanilines.[1] He suggested that the nuclear nitration of aniline derivatives that can easily form nitro-amines may proceed by intramolecular rearrangement of first-formed nitro-amines.[2] Holleman *et al.* cast doubt on this concept by showing that the *C*-nitroanilines are formed in different proportions by the rearrangement of *N*-nitroaniline, and by the direct nitration of aniline.[3] However, this work left some doubt, because the nitrations of aromatic amines are notable for the fact that the proportions of isomers formed vary markedly with the conditions, and the authors used essentially different conditions for their rearrangement and nitration. This hole in the evidence was plugged by Hughes and Jones, who obtained the following, quite different, proportions of isomers for rearrangement and for nitration in the same conditions, namely, in sulphuric acid monohydrate at its freezing-point:[4]

Rearrangement of *N*-nitroaniline	*ortho*, 93%;	*meta*, 0%;	*para*, 7%
Nitration of aniline	,, 6%;	,, 34%;	,, 59%

It was thus made clear that the nuclear substitution is not a rearrangement in disguise, as Bamberger thought. The complementary question of whether the rearrangement is a nuclear substitution in disguise had already been raised by Orton's demonstration that the

* Part I, *J.*, 1950, 2678.

[1] Bamberger, *Ber.*, 1893, **26**, 471, 485; 1894, **27**, 359.
[2] Bamberger, *Ber.*, 1894, **27**, 584; 1895, **28**, 399; Bamberger and Hoff, *Ber.*, 1897, **30**, 1248; *Annalen*, 1900, **311**, 91.
[3] Holleman, Hartogs, and Linden, *Ber.*, 1911, **44**, 704.
[4] Hughes and G. T. Jones, *J.*, 1950, 2678.

XUM

rearrangement of aromatic chloro-amines normally proceeds by an acidolysis to form chlorine, which then effects nuclear chlorination.[5] Bradfield and Orton looked into nitro-amine rearrangements from this point of view, and concluded that, for the most part, they were not analogous.[6] For although they are general-acid catalysed, and although nitro-amines are in general reversibly acidolysed to form nitric acid, the authors could not establish that nitric acid is "invariably and normally" formed when nitro-amines rearrange. Hughes and Jones supplemented this evidence by showing that, whilst in some such rearrangements free nitric acid is not formed fast enough, in others it is freely formed but does not nitrate the aromatic nucleus fast enough to be made responsible for the products of the rearrangements.[4] It thus appeared that typical nitro-amine rearrangements proceed mainly independently of successive acidolysis and nuclear nitration, and therefore by some intramolecular mechanism, presumably, in view of the acid catalysis, an intramolecular rearrangement of the ionic conjugate acid of the nitro-amine.

None of the work surveyed in the preceding paragraph was quantitative enough to yield any conclusions except with respect to a preponderating proportion of the product of a rearrangement, *i.e.*, the main bulk of the principal isomer formed by rearrangement. It helped the concept, that at least this much of the reaction is intramolecular, to note that principal isomers formed in aryl nitro-amine rearrangements are always *ortho*-nitroanilines. A theory of these rearrangements was proposed to the effect that the ionic conjugate acid of the nitro-amine passes its nitro-group to the *ortho*-position by way of a rearrangement of the nitro-amine to a nitrito-amine, in which the nitrito-group could then form a bridge between the nitrogen and the *ortho*-carbon atom, and so migrate to *ortho*-carbon.[7]

The two further questions which arose can be stated with specific reference to the prototype example, the rearrangement of *N*-nitroaniline. It yields 93% of *o*-nitroaniline. We can accept, on the evidence cited, the conclusion that most of this is produced by an intramolecular rearrangement. But is it all produced thus? And how does the 7% of *p*-nitroaniline arise? Two such small proportions of the total product as the last few units % of the *o*-nitroaniline, and the whole of the *p*-nitroaniline, might conceivably be formed, concurrently with the main intramolecular reaction, by successive acidolysis and nuclear nitration. The attraction of this idea is that, if it were true, we should be relieved of the necessity either to extend the already-mentioned theory of the *ortho*-rearrangement or to invent some other theory to cover the formation of the *para*-by-product. The difficulty with the hypothesis that the *p*-nitroaniline arises from acidolysis and nuclear nitration, is that one would then expect some *m*-nitroaniline to accompany the other isomers. Actually Holleman, Hartogs, and Linden reported the presence of about half as much *m*- as of *p*-nitroaniline, but Hughes and Jones, whose work is thought to have been more accurate, found no *m*-nitroaniline at all.

In order to answer definitely the above two questions it was necessary to study quantitatively the distribution, after rearrangement, of a nitrogen-isotopic label appropriately introduced among the reactants. *N*-Nitroaniline was rearranged in aqueous sulphuric acid in the presence of some nitric acid containing an enhanced proportion of ^{15}N. Obviously, any acidolytic nitric acid formed from the nitro-amine would mix with this labelled nitric acid, and any subsequent nuclear nitration would carry the label into the formed nitroanilines.

Hughes and Jones found that *N*-nitroaniline is rearranged smoothly and quantitatively in cold 84% aqueous sulphuric acid. We confirmed this, but found in preparatory experiments that by-products are formed when potassium nitrate is added. Evidently some nitrating or other reactions of the introduced nitric acid with either the nitro-amine or its

[5] Orton, *J.*, 1902, **81**, 490, 806; 1905, **87**, 389; 1907, **91**, 146; 1908, **93**, 725; *Rep. Brit. Assoc.*, 1912, 117.

[6] Bradfield and Orton, *J.*, 1929, 915.

[7] Hughes, cited in Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, New York, 1953, p. 628; cf. Hughes and Ingold, *Quart. Rev.*, 1952, **6**, 51.

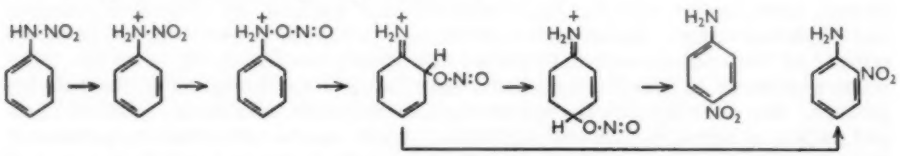
XUM

rearrangement products (reactions which were not necessarily involved in the rearrangement) were now running concurrently with the rearrangement. However, we found that this disturbance disappeared when we used more dilute acid, and, in particular, that, in 74% aqueous sulphuric acid at −20°, the rearrangement is smooth and quantitative, both in the absence and in the presence of added potassium nitrate.

These were therefore the conditions chosen for the experiments on the uptake in rearrangement of a nitrogen-isotopic label originally introduced in added potassium nitrate. The rearrangement product formed in such conditions was chromatographed on alumina. By far the most extensive deposit was *o*-nitroaniline. A pure sample of this, obtained by elution, was isotopically normal in nitrogen. Had 2% of the *o*-nitroaniline, equivalent to *ca.* 2% of the total rearrangement product, contained a nitro-group carried in from free nitric acid, this would have been noticeable in the mass-spectrographic analysis.

The *p*-nitroaniline was found concentrated in the tail of the chromatogram, and, as eluted, contained some residual *o*-nitro-isomer. In view of the isotopic normality of the latter, it was decided to analyse this *para*-concentrate directly, rather than to re-chromatograph it. First, as to the isomer proportions, analyses by freezing-point and by infrared spectrum agreed in giving the composition as 76% of *p*-nitroaniline plus 24% of *o*-nitroaniline. Then, as to isotopic composition, the normal nitrogen abundances were found. Had 1% of the *p*-nitroaniline, equivalent to 0·07% of total rearranged isomers, contained a nitro-group derived from free nitric acid, this would have been detected.

This work shows that the total products of the rearrangement of *N*-nitroaniline, including all the *o*-nitroaniline, and the by-product of *p*-nitroaniline, arise intramolecularly. In extension of the ideas relating to the *ortho*-rearrangement, the suggestion has been made that, just as, on the addition of a proton to the amino-nitrogen atom of the nitro-amine, the nitro-group, after becoming a nitrito-group, can bridge the amino-nitrogen and the *ortho*-carbon atom and can thus achieve transfer to the *ortho*-position, so, after the transfer, but before loss of the proton from the *ortho*-carbon atom, the same nitrito-group can alternatively bridge the *ortho*- and the *para*-carbon atom, and can thus accomplish the further step of transfer to the *para*-position: [8]



In principle, this hypothesis can be checked by means of the isotope effect of *ortho*-deuterium on the isomer ratio of the products of rearrangement, and experiments in this direction are being pursued.

Experimental

^{15}N-Enriched Potassium Nitrate.—This was prepared from ^{15}N-enriched ammonium chloride by carrying the ammonia from a basified solution in excess of oxygen over a platinum coil at 640° and trapping the oxides of nitrogen in potassium hydroxide. The abundance of ^{15}N in the nitrate was 2·95 atoms % in excess of normal. The proportion of nitrite, present as an impurity in the nitrate, was a few units per cent., which it was not considered necessary to remove. The nitrate also contained a little sulphate from the sulphuric acid used to neutralise the slight excess of alkali employed.

Rearrangement of N-Nitroaniline.—The nitro-amine (10 mmols.) was slowly added with stirring to a solution of potassium nitrate (0·75 mmol.), containing a ^{15}N-abundance of 2·95 atoms % in excess of normal, in aqueous sulphuric acid (25 ml.) containing 74% by weight of sulphuric acid at −20°. After stirring had been continued for a further 15 min., the solution was allowed to warm and was then diluted with ice-water (250 ml.). The product was extracted with chloroform, and the combined extracts were concentrated to about 10 ml., and then put

[8] Brownstein, Bunton, and Hughes, *Chem. and Ind.*, 1956, 981.

one-half on each of two alumina columns. Most of the *o*-nitroaniline (m. p. 68°) was washed out with 10 l. of benzene–light petroleum (30–70, v/v). The rest of the adsorbate was removed in benzene, and this eluate, after concentration, was put on a similar column. After development of the chromatogram with benzene (7 l.), this column was ejected and cut up, and the portions were extracted with acetone. A *p*-nitroaniline concentrate (m. p. 131°) was thus obtained, which was shown by both f. p. and infrared spectrum to contain 76% of the *p*-isomer.

Mass-spectrometric Analysis.—Measurements of the isotopic composition of nitrogen were made on nitrogen gas obtained from ammonia. From potassium nitrate, the ammonia was produced by reduction with Devarda's alloy. From *o*- or *p*-nitroaniline, or from mixtures of them, the ammonia was prepared as follows. To the sample (0·1 g.) were added glucose (1 g.), potassium sulphate (4 g.), some copper sulphate, and concentrated sulphuric acid (30 ml.). The mixture was digested until pale yellow (about 2 hr.), and thereafter for a further 15 min. After 50% potassium hydroxide (100 ml.) had been added, the liberated ammonia was collected in dilute sulphuric acid. This procedure converted both nitrogen atoms of the nitroanilines quantitatively into ammonia.

The ammonium sulphate was converted into nitrogen gas by treating its solution with one of sodium hypobromite in a vacuum.[9] The evolved nitrogen was analysed mass-spectrometrically.

The nitroanilines, isolated from the product of rearrangement of *N*-nitroaniline in aqueous sulphuric acid in the presence of ^{15}N-enriched potassium nitrate, had contents of ^{15}N slightly lower than that of a sample of nitrogen from a cylinder. The latter nitrogen being taken as normal, the recovered *o*-nitroaniline had a ^{15}N-abundance of −0·004 and −0·002 atom % excess, the former figure applying to a preliminary experiment on one-tenth of the scale of the final one. The figures obtained for the ^{15}N-abundance in the *p*-nitroaniline concentrate were −0·003 and −0·002 atoms % excess.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1. [*Received, July 25th*, 1958.]

[9] Rittenberg, "Preparation and Measurement of Isotopic Tracers," J. W. Edwards, Ann Arbor, Michigan, 1948, p. 36.

---

884. *Nitration at Nitrogen and Oxygen Centres. Part I. Kinetics and Mechanism of the Conversion of Secondary Amines into Nitroamines.*

By E. D. HUGHES, SIR CHRISTOPHER INGOLD, and R. B. PEARSON.

The *N*-nitration of *N*-methyl-2 : 4 : 6-trinitroaniline by nitric acid in constant excess in nitromethane of not-too-high water-content is of zeroth order and, at not-too-high concentrations of nitric acid, the absolute rate of the nitration is identical with the common rate of nitration of aromatic hydrocarbons under the same conditions. Small additions of sulphuric acid increase, of nitrate ions reduce, and of water do not change, the zeroth-order rate, but larger additions of water increase rate, with maintenance of the zeroth-order form, and still larger ones change the kinetics to first-order form, with reduction in the absolute rate during the kinetic transition, and in the first-order rate-constant after it is completed. These effects fully establish the nitronium-ion mechanism for this *N*-nitration.

Two successive steps of nitration of *N*-methyl-2 : 4-dinitroaniline occur in similar conditions. The first step is an *N*-nitration, the kinetic characteristics of which, as far as studied, are practically identical with those of the nitration just described. The second kinetic step is stoicheiometrically a *C*-nitration, and is observed only in first-order form. Almost certainly the rate-controlling process here is an intramolecular rearrangement, in which the *N*-nitro-group moves into the aromatic ring, this slow reaction then being very quickly succeeded by another *N*-nitration.

ELECTROPHILIC substitution has hitherto been studied largely in the form of aromatic substitution, where the attack by the substituting agent is on the unsaturation electrons, *i.e.*, conjugated carbon 2*p* electrons. Since non-bonding 2*p* electrons of nitrogen and

XUM

oxygen can participate deeply in such conjugation, we should expect them to share many properties with the unsaturation 2*p* electrons of carbon, including general vulnerability to electrophilic substituting agents. Indeed, for a given substitution of this class, *e.g.*, nitration, nitrosation, or chlorination, we should expect the pattern of mechanisms to be much the same for *C*-, *N*-, and *O*-substitutions.

Nitration has proved to be one of the simpler forms of electrophilic aromatic substitution, because it is dominated by one outstanding mechanism, that of the nitronium ion. Aromatic nitration through attack of the nitronium ion was kinetically demonstrated, at first in non-hydroxylic, and in hydroxylic but non-aqueous solvents,[1,2] and, more recently, even in solvent water.[3]

$$HNO_3 + HNO_3 \underset{-1}{\overset{+1}{\rightleftharpoons}} H_2NO_3^+ + NO_3^- \text{ (fast)} \quad . . . . . \quad \Big\}$$

$$H_2NO_3^+ \underset{-2}{\overset{+2}{\rightleftharpoons}} NO_2^+ + H_2O \text{ (slow)} \quad . . . . . \quad \Big\} \text{(I)}$$

$$NO_2^+ + XH \xrightarrow{3} XH{\cdot}NO_2^+ \text{ (slow)} \quad . . . . . \quad \Big\}$$

$$XH{\cdot}NO_2^+ + NO_3^- \xrightarrow{4} X{\cdot}NO_2 + HNO_3 \text{ (fast)} \quad . . . . . \quad \Big\}$$

We here apply the general method of these demonstrations to *N*-nitration, which again proves to be an affair of the nitronium ion. The principle of the method can be most easily appreciated by recalling the conclusion to which it led concerning the mechanism of aromatic nitration. This conclusion is expressed in scheme (I), XH replacing ArH, for convenience. There are four stages. The nitronium ion is formed in two steps, of which the former, a protonation, is always fast. Then the substitution in the substrate goes in two steps, of which the latter, a deprotonation, is always fast. The intermediate steps, **2** and **3**, are in principle slow, and, in any particular case, the kinetic form depends on which of them is rate-controlling. With a sufficient concentration of a sufficiently reactive substrate, and in a not-too-aqueous medium, step **3** prevails over step -2 as a means of consumption of formed nitronium ion, so that the latter reacts, as fast as it is formed, with the substrate, and the measured nitration rate is the rate of its formation in step $+2$. This rate in turn is proportional to the stationary concentration of nitric acidium ion, and is therefore increased by added small amounts of a very strong acid, such as sulphuric acid, and is decreased by added nitrate ions. But as long as the nitronium ions are trapped almost wholly by the substrate, the measured rate must be independent of the concentration and nature of the latter: it will be of zeroth-order in the substrate.

The other limiting situation is that in which the substrate is so unreactive, or so dilute, or the medium is so aqueous, that step -2 prevails over step **3** in the consumption of nitronium ion. The latter is then established in a stationary concentration, not sensibly depleted by the slow withdrawal of material by the substrate; the rate of such withdrawal becomes proportional to the concentration, and dependent on the nature, of the substrate. The rate still depends on a pre-equilibrium protonation, and hence will be affected as before by an added strong acid, and by added nitrate. But it will now be of first-order in the substrate, and the rate-constants applying to different substrates will reflect their intrinsic reactivities.

A firm proof of mechanism requires the observation of both limiting kinetic forms, and of the transition between them, effected, as this may be, by changing the trapping power for nitronium ion either of the substrate, or of the water, *i.e.*, by changing the balance of competition between these two consumers of formed nitronium ion.

These principles are here applied to the conversion of secondary amines into nitroamines by means of nitric acid in constant excess in solvent nitromethane. In this polar,

[1] Benford and Ingold, *J.*, 1938, 929.
[2] Hughes, Ingold, and Reed, *J.*, 1950, 2400.
[3] Bunton, Halevi, and Llewellyn, *J.*, 1952, 4913; Bunton and Halevi, *ibid.*, p. 4917; Bunton and Stedman, *J.*, 1958, 2420.

XUM

but initially non-aqueous, solvent, the concentration of water during nitration is of the same order of magnitude as that of the material being nitrated; and so the water sets a relatively easy standard of trapping efficiency for the substrate to overcome when zeroth-order kinetics are required to be established. Our secondary amines were, in fact, reactive enough to prevail as trapping agents at this competitive level. We could then raise the competitive standard by adding water, until the amines lost their predominating position as trapping agents. Thus we could observe the transition to first-order kinetic form.

Kinetics were followed by dilatometry, subject to check by chemical examination of the products. In both principle and technique, methods were modelled on those formerly used to establish mechanism in aromatic nitration, although some refinement of apparatus was introduced. A preliminary note on the present work has appeared.[4]

(*A*) *Conversion of* N-*Methyl*-2 : 4 : 6-*trinitroaniline into* N-*Methyl*-N : 2 : 4 : 6-*tetranitroaniline.*—This *N*-nitration was chosen first for its expected simplicity, inasmuch as the secondary amine is so weakly basic that heavy protonation in nitration conditions seemed likely to be avoidable. Moreover, the nitro-amine could not undergo rearrangement, and the aromatic ring was incapable of being itself nitrated.

(1) *Kinetic form. Effect of substrate concentration.* The nitration in nitromethane is associated with a contraction. It is only about one-quarter of that accompanying the nitration of toluene, but is large enough for easy measurement.

A typical reaction–time curve, obtained dilatometrically, for nitration in initially dry nitromethane, is shown in Fig. 1. Similar curves were obtained in many runs covering initial substrate concentrations from about 0·04 to 0·16M, sometimes also with other added substances. The reaction is clearly of zeroth order in substrate.

Since each run has zeroth-order form, the zeroth-order rate constant, as deduced from the constant slope of the curve, should be independent of the initial concentration of the substrate at concentrations over which the zeroth-order law prevails. This is so, as is illustrated in Table 1, the mean value of 10^5k_0 being 2·89 moles $l.^{-1}$ $sec.^{-1}$.

After a number of runs, the contents of the dilatometer were examined chemically. A high yield of *N*-methyl-*N* : 2 : 4 : 6-tetranitroaniline was invariably isolated.

(2) *Comparison with rate of nitration of toluene.* The rate of nitration of *N*-methyl-2 : 4 : 6-trinitroaniline increases steeply with increasing concentration of nitric acid. A quite similar behaviour has been repeatedly observed in aromatic nitration, for example, of toluene. In 2M-nitric acid the absolute nitration rates of the secondary amine and of toluene are identical (Table 2).

TABLE 1. *Zeroth-order rate-constants* (k_0 *in moles* $l.^{-1}$ $sec.^{-1}$) *for nitration of* N-*methyl*-2 : 4 : 6-*trinitroaniline by* 3·0M-*nitric acid in nitromethane at* 25°.

$[Amine]_0$ ...	0·0314	0·0458	0·0688	0·0752	0·0786	0·0832	0·0887	0·127	0·150	0·163
10^5k_0	2·75	2·75	2·80	2·85	2·92	2·95	3·02	2·95	3·01	2·89

TABLE 2. *Zeroth-order rate-constants* (k_0 *in moles* $l.^{-1}$ $sec.^{-1}$) *for nitration of* N-*methyl*-2 : 4 : 6-*trinitroaniline and of toluene* (*initially about* 0·1M) *by nitric acid in nitromethane at* 25°.

$[HNO_3]$	2·0	2·5	3·0	3·5	4·0	4·5
10^5k_0 (amine)	0·675	1·41	2·89	6·04	9·64	14·9
,, (toluene) ...	0·688	1·69	3·34	6·80 *	12·7	—

* Value for ethylbenzene.

At the higher nitric acid concentrations the rate for nitration of the amine drops behind the rate for benzenoid hydrocarbons. The cause of this is not established, but it may be that the amine becomes partly protected by protonation at the higher acid concentrations. There is some evidence [4] that the deviation becomes diminished in the presence of so-called nitrous acid. This is really dinitrogen tetroxide, partly in ionised

[4] Blackall and Hughes, *Nature*, 1952, **170**, 972.

XUM

form,[5] and hence leads to the presence of nitrate ion, which, as the lyate ion of the system, must reduce its acidity.

(3) *Kinetic effects of added solutes.* When sulphuric acid is added to the system, nitration is accelerated without change to its zeroth-order form (Table 3). Above a certain small concentration of sulphuric acid, the rate increase is linear with the concentration (Fig. 2). We interpret the change in rate as reflecting the change in the stationary concentration of nitric acidium ion, from which is derived the nitronium ion, the rate of production of which is measured in the observed nitration. Hence, we should expect the linear law to hold only after enough of the strong acid has been added fully to suppress formation of nitric acidium ion by autoprotolysis of the nitric acid, *i.e.*, to secure

FIG. 1. *Zeroth-order nitration of N-methyl-2 : 4 : 6-trinitroaniline* (0·16M) *by nitric acid* (4·0M) *in nitromethane at* 25°.

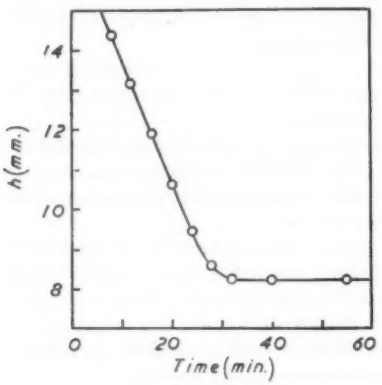
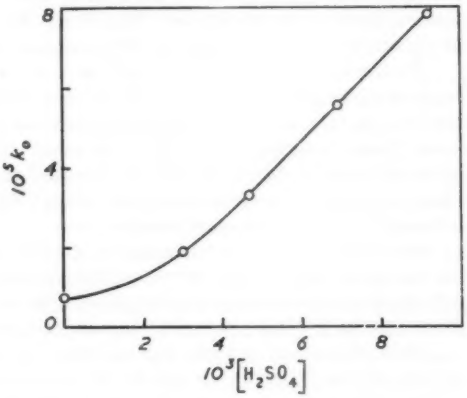


FIG. 2. *Effect of sulphuric acid on zeroth-order rate of nitration of N-methyl-2 : 4 : 6-trinitroaniline* (0·05M) *by nitric acid* (2·0M) *in nitromethane at* 25°.



practically complete protonation of the nitrate ions thus formed. Accordingly, the accelerating effect of progressive addition of the strong acid should be expressed by a curve, such as is in Fig. 2, the slope of which is only somewhat slowly built up to that of its linear portion.

As is illustrated in Table 3, a substantial accelerating effect is experienced when sodium perchlorate is added to the original system. We assume that, at the concentrations used, the salt would be largely present as dissociated ions, and we interpret the acceleration as a normal salt effect on a reaction, the kinetically significant part of which, *i.e.*, the part up to and including the slow step, is producing ions (nitronium and nitrate) from initially neutral species (nitric acid molecules).

The addition of sodium nitrate to the original system produces a retardation, as is also shown in Table 3. This must be the residue of a larger specific retardation which outweighs the accelerating normal effect of the salt. Although we have not enough data to allow a quantitative separation of these two effects, the specific retardation is qualitatively consistent with its interpretation as a suppression by added nitrate ions of the production of nitric acidium ion by the autoprotolysis of nitric acid.

(4) *Kinetic transition from zeroth to first order.* When, to the original system, water was added in successively increasing quantities, the following kinetic changes were observed. In the millimolar and centimolar ranges of concentration, the ranges in which substantial kinetic effects were produced by the added solutes considered in the preceding sub-section, added water produced no observable kinetic effect. As water does not appear

[5] Goulden and Millen, *J.*, 1950, 2620.

in the equation for the autoprotolysis equilibrium, the only pre-equilibrium in zeroth-order nitration, this is very reasonable. Near the concentration 0·1M-water, a definite acceleration appeared, which we view as an ordinary medium effect; but there was still no detectable disturbance to the zeroth-order form of the reaction. Since the kinetically significant part of a zeroth-order nitration produces ions from originally neutral species, a highly polar co-solvent, such as water, should be expected to accelerate the reaction.

TABLE 3. *Effects of added sulphuric acid, sodium perchlorate, and sodium nitrate on the zeroth-order rate-constants (k_0 in moles $l.^{-1}$ $sec.^{-1}$) of nitration of* N-*methyl*-2 : 4 : 6-*trinitroaniline* (*initially about* 0·05M) *by nitric acid in nitromethane at* 25°.

$[HNO_3] = 2·0$M		$[HNO_3] = 3·0$M		$[HNO_3] = 3·0$M	
$[H_2SO_4]$	10^5k_0	$[NaClO_4]$	10^5k_0	$[NaNO_3]$	10^5k_0
0	0·680	0	2·75	0	2·75
0·00301	1·89	0·00315	3·16	0·00320	2·03
0·00469	3·29	0·00643	3·47	0·00784	1·53
0·00690	5·54	0·00719	3·82	0·0120	1·42
0·00920	7·81			0·0177	1·31

And since water is still not a pre-equilibrium product, it has no specific kinetic effect which could counter this general co-solvent effect. The idea that added water can, in certain circumstances, accelerate nitration, though unconventional, is thus rational. However, when water was added above a concentration of about 0·2M, the absolute rate began to fall, and the reaction simultaneously began to lose its zeroth-order form. As the water concentration was further increased the rate fell sharply, and the kinetic order rose from zero towards unity, at first near the " tail " of reaction, and later throughout its course. At 0·8M-water, a first-order kinetic form had been established throughout reaction with good approximation. On still further increase of the water concentration, the rate, now specifiable by means of a first-order rate-constant, continued to fall, though the first-order law remained in force to the highest water-concentration investigated, 1·0M. This first-order kinetic form of nitration is illustrated in Fig. 3. We can understand why water retards the first-order reaction, although it mildy accelerates the zeroth-order reaction, by noting that, in the first-order reaction, water will have not only its general co-solvent effect, but also a specific retarding effect, because not only the autoprotolysis, but also the cationic dehydration, are now included in the pre-equilibrium, and, in this enlarged pre-equilibrium system, water is a product. Some rate-constants illustrating the main steps in these kinetic effects are assembled in Table 4.

TABLE 4. *Zeroth- and first-order rate-constants (k_0 in moles $l.^{-1}$ $sec.^{-1}$ and k_1 in $sec.^{-1}$) of nitration of* N-*methyl*-2 : 4 : 6-*trinitroaniline* (*about* 0·05M) *by nitric acid* (3·0M) *at* 25° *in nitromethane containing various concentrations of initially added water.*

$[H_2O]$ *	10^5k_0	Order	$[H_2O]$ *	10^4k_1	Order
—	2·75	0	0·794	~2·61	impure
0·149	3·29	0	0·825	1·96	1
0·228	3·23	0	0·972	1·40	1
0·469	~1·78	impure	1·02	1·34	1
0·610	~0·99	impure			

* *Added* water.

(5) *Mechanism of* N-*nitration.* The preceding four sections cover all the important points of evidence on which the mechanism of scheme I [with X = 2 : 4 : 6-$(NO_2)_3C_6H_2$·NMe] may be based: thus *N*-nitration is certainly proceeding by attack of pre-formed nitronium ion on the unshared electrons of the amino-nitrogen atom.

(6) *Comparison of reactivity of amine and hydrocarbons.* It is interesting to compare the kinetic reactivity towards nitronium ion of these unshared nitrogen electrons with that of carbon unsaturation electrons in an aromatic hydrocarbon. This we can do by comparing the first-order rate constants for nitration of the amine, and of one or more aromatic

XUM

hydrocarbons, in nitromethane containing approximately 1M-added water. For $[H_2O]$ = 0·972, some first-order rate constants, expressed as 10^4k_1, with k_1 in sec.$^{-1}$, are: Benzene 1·0; *N*-methyl-2 : 4 : 6-trinitroaniline, 1·4; toluene, 23·4. The amine thus lies between benzene and toluene, though it is closer to benzene in kinetic affinity for the nitronium ion. But it must be much more basic than either hydrocarbon.

(*B*) *Conversion of* N-*Methyl*-2 : 4-*dinitroaniline successively into* N-*Methyl*-N : 2 : 4-*trinitroaniline and* N-*Methyl*-N : 2 : 4 : 6-*tetranitroaniline.*—(1) *The first step of nitration.* When *N*-methyl-2 : 4-dinitroaniline (0·05—0·15M) is nitrated by nitric acid (3·0—4·0M) in nitromethane at 25°, two kinetically distinct steps are seen, each marked by a contraction. In a typical experiment, the volume–time curve fell linearly for the first half-hour, with a slope similar to that which would have applied to the *N*-nitration described in Section (*A*). Then the slope changed abruptly, but not, as in the reaction of Section (*A*), to horizontality: the new direction had a small finite slope, and actually marked the start of an extended further curve, which continued to fall slowly, with exponentially diminishing slope, for many hours. We thus had a fast initial reaction of zeroth-order, succeeded by a slow continuing reaction of first order.

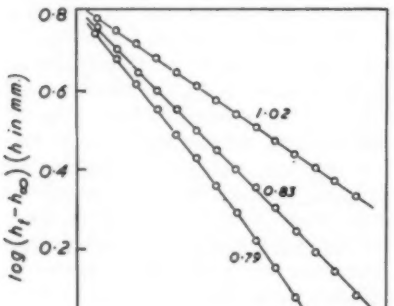


FIG. 3. *First-order nitration of* N-*methyl*-2 : 4 : 6-*trinitroaniline* (~0·05M) *by nitric acid* (3·0M) *in nitromethane at* 25°. *The figures by the curves are concentrations of added water. One curve is not straight* (*cf. Table* 4).

On stopping experiments at the break in the curve, we found that the product at that point was *N*-methyl-*N* : 2 : 4-trinitroaniline. Thus the initial reaction is an *N*-nitration. And, like the *N*-nitration described in Section (*A*), it is of zeroth-order in the substrate, when conducted in initially dry nitromethane.

This being so, we might have expected that the absolute rate of *N*-nitration of the dinitro-amine and of the trinitro-amine would be the same in the same conditions. However, as shown in Table 5, this is not the case for the conditions specified; the dinitro-amine is *N*-nitrated somewhat more slowly than is the trinitro-amine. This may be a matter of protection by protonation of some of the amine from attack by the nitronium ion. At a given concentration of nitric acid, a fixed fraction of the stoicheiometric total of either amine will be present in free-basic form, and this fraction will remain constant as the stoicheiometric total of amine becomes consumed in reaction. With, for example, 3M-nitric acid, the fraction of trinitro-amine thus left free is probably high, though we saw signs of partial protection against nitration at this acidity in Section (*A*2). The dinitro-amine is, however, a considerably stronger base, and so it seems likely that more of it will be protonated, and less left in free-basic form in the conditions specified in Table 5. This might explain the rate differences.

(2) *The second step of nitration.* By isolating the material present when the kinetic form changes, we found that the second step starts from *N*-methyl-*N* : 2 : 4-trinitroaniline. By isolation of the material present at the end of the second step, it was found that the

final product is *N*-methyl-*N* : 2 : 4 : 6-tetranitroaniline. Stoicheiometrically the second kinetic step is a *C*-nitration. It will suffice thus to consider it at first, though we shall see later that appearances may be deceptive.

For greater convenience, two changes were now made in the conditions. First, to provide a sharper start, we introduced *N*-methyl-*N* : 2 : 4-trinitroaniline as such, instead of

TABLE 5. *Zeroth-order rate-constants* (k_0 *in moles* $l.^{-1}$ $sec.^{-1}$) *for the* N-*nitration of* N-*methyl*-2 : 4-*dinitro- and* N-*methyl*-2 : 4 : 6-*trinitro-aniline in nitromethane at* 25°.

$[Amine]_0$	$[HNO_3]$	10^5k_0 (dinitro-amine)	10^5k_0 (trinitro-amine)
0·05	3·0	2·13	2·75
0·10, 0·14	4·0	7·2	9·6

TABLE 6. *First-order rate-constants* (k_1 *in* $sec.^{-1}$) *for the* C-*nitration of* N-*methyl*-N : 2 : 4-*trinitroaniline* (*initially* 0·1M *throughout*) *by nitric acid in nitromethane at* 25°, *and the kinetic effects of added sulphuric acid, sodium perchlorate, potassium nitrate, and water.*

$[HNO_3]$	5·0	5·5	6·0	6·5	7·0	7·5	8·0
10^4k_1	2·17	2·77	3·85	5·45	7·52	10·6	13·7

$[HNO_3] = 5·5$		$[HNO_3] = 7·0$		$[HNO_3] = 7·5$		$[HNO_3] = 7·5$	
$[H_2SO_4]$	10^4k_1	$[NaClO_4]$	10^4k_1	$[KNO_3]$	10^4k_1	$[H_2O]$	10^4k_1
—	2·77	—	7·52	—	10·6	—	10·6
0·00146	3·60	0·00263	7·87	0·00168	9·79	0·100	9·7
0·00245	4·05	0·00485	8·45	0·00323	7·20	0·150	10·0
0·00410	6·43	0·00918	9·41	0·00623	6·40	0·292	9·0
0·00572	8·02	0·0115	9·88	0·0104	5·34	0·453	5·95
0·00580	8·25	0·0171	10·5	0·0154	4·42	0·594	5·18
0·00874	16·3			0·0205	3·52	0·748	4·08

waiting for its concentration to be built up by the original *N*-nitration. Then, since, in the conditions for the observation of this *N*-nitration, namely, by the use of 3—4M-nitric acid in nitromethane at 25°, the ensuing *C*-nitration is inconveniently slow, the *C*-nitration of introduced *N*-methyl-*N* : 2 : 4-trinitroaniline was studied with concentrations of nitric acid raised to 5—8M.

The *C*-nitration is approximately of first order in the substrate, though this kinetic law loses accuracy at late times. As shown in Table 6, the rates increase steeply with increasing concentration of nitric acid.

Some observations on the kinetic effect of added substances are recorded in Table 6. The reaction is strongly accelerated by added small amounts of sulphuric acid. It is moderately accelerated by added sodium perchlorate. Nevertheless, it is strongly retarded by added potassium nitrate. Relative to these additives, water has only a trivial kinetic effect, though, when added in excess of 0·2M, it produces a retardation. All these rate effects occur without change to the essentially first-order form of the reaction.

These kinetic results are closely in line with what is to be expected for *C*-nitration by the nitronium-ion mechanism. In zeroth-order nitration the rate of formation of nitronium ion, and in first-order nitration the stationary concentration of nitronium ion, are both proportional to the stationary concentration of its precursor, the nitric acidium ion, formed, as this is, by the preliminary protonation of nitric acid. The addition of a very strong acid, such as sulphuric acid, must raise the stationary concentration of nitric acidium ion. The addition of the strongest admissible base, the lyate ion of the system, namely, nitrate ion, must reduce it. Apart from such specific effects, neutral salts will raise the stationary concentration of the cation by the electrostatic effect of their ionic strength. Water will not directly affect the concentration of nitric acidium ion until it is in sufficient concentration to dominate autoprotolytic nitrate ions as a base, but it will then cause retardation.

Thus, our kinetic results are entirely consistent with the view that what is being measured is the rate of a *C*-nitration, which is what the reaction is stoicheiometrically, a

nitration proceeding with first-order kinetics, as is to be expected for *C*-nitration in an aromatic nucleus already deactivated with two nuclear nitro-groups.

(3) *An alternative interpretation of the second kinetic step.* This is that the reaction measured is a rearrangement of *N*-methyl-*N* : 2 : 4-trinitroaniline to *N*-methyl-2 : 4 : 6-trinitroaniline, and that this change is followed by a relatively rapid *N*-nitration of its product to give *N*-methyl-*N* : 2 : 4 : 6-tetranitroaniline. The final *N*-nitration would certainly be relatively rapid, according to the specific investigation of it described in Section (*A*). It is necessary to try to decide whether the rate-controlling process is indeed a *C*-nitration, or is such a rearrangement of a nitro-amine.

Let us first consider the bearing of the kinetic results on this question. Since the original demonstration of the mechanism of aromatic nitration by nitronium ion, including the mechanism of formation of nitronium ion, was given largely on the basis of a pattern of kinetic results similar to those described in the preceding sub-section, it has been all too easy to accept the observation of such a kinetic pattern as pointing to a nitronium-ion process, supposing that the reaction being studied is stoicheiometrically a nitration. However, what the kinetic pattern, which has been encountered several times, discloses is that the sequence of reactions under observation is based on a pre-equilibrium protonation of something—so far as this evidence alone goes, of anything. Some collateral consideration must be imported in order to identify what is being protonated, and in the prototype investigation of aromatic nitration it was indeed thus that the protonated material was identified as molecular nitric acid. For example, when the measured reaction was a zeroth-order nitration of *any* substrate, the protonated substance has to be nitric acid because the substrate is not kinetically involved. When the measured reaction is a first-order nitration of a non-basic substrate, such as an aromatic hydrocarbon or halogenohydrocarbon, the protonated substance still has to be nitric acid, because (though for a different reason) there is still no chemically sensible alternative. When the measured reaction is a first-order nitration of a base, such as an amine, the protonated substance even yet has to be nitric acid, because protonation of the substrate, though possible, would be (and probably is) inhibitory. However, if we should be observing a first-order rearrangement catalysed by nitric acid, then a kinetic disclosure of pre-equilibrium protonation would have to be interpreted as protonation of the substrate itself. Should the rate-controlling process be indeed a rearrangement, proceeding through a conjugate acid formed from the substrate with nitric acid as the proton-donor, then the kinetic findings would be ***exactly the same*** as for a rate-controlling first-order nitration by nitronium ion formed in consequence of the autoprotolysis of nitric acid. Equilibria of this form, $AH^+ + B \rightleftharpoons A + BH^+$ generally preclude purely kinetic information as to whether A or B receives a proton, and thus our kinetic results do not solve the question.

The chemical considerations to be set beside the kinetic are those derived from past investigations concerning the rearrangement of aromatic nitro-amines,[6] and the order of the successive steps in the polynitration of *N*-methylaniline.[7]

As to the former, the rearrangements of aromatic nitro-amines, which are acid-catalysed, are intramolecular. If the catalyst is nitric acid, any concomitant hydrolysis of the *N*-nitro-group, *i.e.*, any reversibility in *N*-nitration, is likely to be inappreciable. With other catalysing acids it may be appreciable, but this does not provide a route of any importance for rearrangement; it simply protects, temporarily, a certain fraction of the original nitro-amine from intramolecular rearrangement, reducing the rate, but not the ultimate extent, of that process; it does not change its intramolecular character.

As to the latter, introduction of the third nuclear nitro-group into the vacant *ortho*-position in the polynitration of *N*-methylaniline is slow and difficult, hardly to be accomplished except by " mixed acid," and certainly not by nitric acid alone under

[6] Hughes and Jones, *J.*, 1950, 2678; Brownstein, Bunton, and Hughes, *Chem. and Ind.*, 1956, 981; *idem*, preceding paper.
[7] Glazer, Hughes, Ingold, James, Jones, and Roberts, *J.*, 1950, 2657.

conditions which suffice for the *N*-nitration of either *N*-methyl-2 : 4-dinitro- or *N*-methyl-2 : 4 : 6-trinitro-aniline. Apart from complications which may arise if nitrous acid is allowed into the system, the later stages of polynitration of *N*-methylaniline were shown to take the following course: *N*-methyl-2 : 4-dinitroaniline is first *N*-nitrated; then the formed *N*-methyl-*N* : 2 : 4-trinitroaniline rearranges to *N*-methyl-2 : 4 : 6-trinitroaniline; and then this is further *N*-nitrated to the final product, *N*-methyl-*N* : 2 : 4 : 6-tetranitro-aniline.

In the light of this evidence, there seems no doubt that the second kinetic step of the double nitration of *N*-methyl-2 : 4-dinitroaniline is actually the nitro-amine rearrangement, which kinetically carries with it a relatively fast subsequent *N*-nitration. Our favoured interpretation of the two kinetic steps may thus be summarised as follows:

Kinetic first step: (i) *N*-Nitration by nitronium ion (somewhat fast; zeroth order).
Kinetic second step: (ii) Rearrangement (acid-catalysed; slow; first order). (iii) As (i).

(*C*) N-*Nitration of Other* N-*Alkylanilines*.—Measurements have been made on the zeroth-order *N*-nitrations of *N*-ethyl-, *N*-*n*-propyl-, and *N*-*n*-butyl-trinitroaniline by 3M-nitric acid in nitromethane at 25°, but the results are so similar to those described in Section *A* that we do not record them.

Measurements have also been made on the *N*-nitration in similar conditions of *N*-*iso*-propyl-2 : 4 : 6-trinitroaniline. In this case the zeroth-order law is not accurately obeyed, the order in substrate rising above zero especially towards the end of reaction. Also, the absolute rate is now only about 0·6 times as large as the nearly common rate applying to the other *N*-alkyl analogues. The beginnings of a transition to first-order kinetics, perhaps on account of steric shielding of the unshared nitrogen electrons, may here be under observation.

Experimental

Materials.—The amines nitrated and the products formed in the work described in Sections *A* and *B* were as previously described.[6,7] Nitric acid was purified as usual by distillation twice with sulphuric acid in all-glass apparatus under an oil-pump vacuum, and stored (white powder) in the dark at −80°: it had its maximum freezing-point, and no nitrous acid was detected. Nitromethane was carefully purified, with gas-chromatography as a preliminary criterion and the nitration rates as a final criterion of purity. The most satisfactory material was obtained with omission of drying with phosphoric oxide and chromatography on alumina, which have sometimes been introduced. After passing nitrogen through the nitromethane under reflux for a day, the sample was dried ($CaSO_4$), filtered, distilled, and refractionated. The water content (Karl Fischer) was about 0·01% and the nitrous acid content [8] about 10^{-6}M. Gas-chromatography revealed no impurity except water, and it was verified by deliberate additions that the common impurities, formaldehyde and formic acid, were not being obscured in the chromatogram by the large peak due to nitromethane. In the few cases in which the presence of nitrous acid was required, it was added as solid dinitrogen tetroxide, prepared and purified in the customary way.

Kinetics.—These were followed essentially by our standard dilatometry.[1] However, the investigation in Part II (following paper) demanded a dilatometric precision at least an order of magnitude higher than previously needed, and most of the results herein recorded were obtained with this improved apparatus.

We gratefully acknowledge the exploratory work by Dr. J. Glazer and Dr. E. L. Blackall.

William Ramsay and Ralph Forster Laboratories,
University College, W.C.1. [*Received, July 25th*, 1958.

[8] Mellon, "Organic Reagents in Organic Analysis," Blakiston Co., Philadelphia, 1941.

XUM

885. *Nitration at Nitrogen and Oxygen Centres. Part II.* Kinetics and Mechanism of the Conversion of Alcohols, Glycols, and Glycerol into their Nitric Esters.*

By Eileen L. Blackall, E. D. Hughes, Sir Christopher Ingold, and R. B. Pearson.

The *O*-nitrations of methyl alcohol, *p*-nitrobenzyl alcohol, ethylene glycol, trimethylene glycol, and also glycerol with respect to its primary hydroxyl groups, with nitric acid in constant excess in solvent nitromethane of not-too-high water-content, are of zeroth-order and identical in absolute rate with one another and with the *N*-nitrations of *N*-methyl-di- or -tri-nitroaniline and with the *C*-nitrations of benzenoid hydrocarbons under the same conditions. For the nitration of methyl alcohol small concentrations of sulphuric acid increase, of nitrate ions decrease, and of water do not change the zeroth-order rate, whilst larger concentrations of water increase it, and still larger concentrations cause a switch from zeroth- to first-order kinetics with reduction in the absolute rate. In the presence of sufficient water to secure first-order kinetics, the rates of attack of nitronium ion on the unsaturated or unshared electrons of carbon, nitrogen, and oxygen in the substances mentioned were compared.

In conditions similar to those of these zeroth-order nitrations, *neo*pentyl alcohol is nitrated in a kinetic form between zeroth and first order, and at a smaller absolute rate, whilst the secondary hydroxyl group, remaining after the nitration of glycerol has completed its zeroth-order course, is nitrated in first-order form, and at a still smaller rate.

As noted in the preceding paper, we expect that, for any one general reaction within the natural family of electrophilic substitutions, for instance, nitration, nitrosation, or chlorination, much the same pattern of available mechanisms will apply to *C*-, *N*-, and *O*-substitutions. In particular, we expect that, since in *C*-nitration the nitronium-ion mechanism is outstandingly important, this mechanism will probably dominate the picture of *N*- and *O*-nitrations.

We are here concerned with *O*-nitrations, particularly with the conversions of alcohols into alkyl nitrates. Until recently, such esterifications with nitric acid seem not to have been generally regarded, at least not automatically, as nitrations. In 1950 Israelashvili suggested that the conversion of starch into its nitrate might be an *O*-nitration.[1] In 1951, Klein and Mentser proved, by the use of isotopically labelled oxygen, that the conversion of cellulose into its nitrate was indeed an *O*-nitration: what was shown was that, for each group C–O–H converted, the replacement was of H by NO_2, with two oxygen atoms from the nitrating medium, not of OH by NO_3, with three oxygen atoms from that source.[2] This work firmly classified the esterifications of alcohols with nitric acid as nitrations, but left untouched the question of nitration mechanism.

The nitronium-ion mechanism of the *O*-nitration of alcohols was first identified[3] in this research by the kinetic method originally developed (refs. 1 and 2 of preceding paper) for the study of aromatic *C*-nitration, the principle of which is to show that a conjugate acid of nitric acid is dehydrated to a nitrating entity, which, according to how we adjust the competitive conditions, can either be recaptured by the water or trapped by the substrate, with consequent change in the kinetic order, first or zeroth, with respect to the substrate. Reference was made in the preliminary account[3] to the nitration of methyl alcohol and several other mono- and poly-hydric alcohols, including glycerol. The great

* Part I, preceding paper.

[1] Israelashvili, *Nature*, 1950, **165**, 666.
[2] Klein and Mentser, *J. Amer. Chem. Soc.*, 1951, **71**, 5888.
[3] Blackall and Hughes, *Nature*, 1952, **170**, 972.

technical importance of the nitration of glycerol for more than a century being considered, it seems curious that the kinetics of the reaction should have been established only lately.

In such work it is usual, for greater convenience in arranging the necessary competitive balance, to work in a medium based on a polar but non-aqueous solvent with a somewhat low content of adventitious or added water, usually not above 1M. However, in 1952, Bunton and Halevi extended the kinetic method of diagnosing mechanism in aromatic nitration to nitrations in aqueous nitric acid, although, of course, in these conditions the standard of competition for nitronium ion set by the water is very much more severe; they were able to show that the nitronium-ion mechanism is still responsible for *C*-nitration, even in these highly aqueous conditions.[4] Concurrently, with Llewellyn, and by the use of isotopically labelled water, they attacked the problem of the mechanism of oxygen exchange between nitric acid and water, that is, of the *O*-nitration of water, in the same aqueous nitric acid media. And from the identity of the absolute rate of exchange in such a medium with the absolute rate in the same medium of an aromatic nitration, so organised that the organic substrate captures almost all the nitronium ion, the kinetic order in substrate becoming zero, they were able to prove that, in aqueous nitric acid containing, say, 60 moles % of water, the nitronium-ion mechanism is responsible for the *O*-nitration of water.[4,5]

Bonner and Frizel recently furnished evidence for the nitronium-ion mechanism in the *O*-nitration of alcohols by nitric acid in an aqueous solution of a very strong acid. They showed that the rate of *O*-nitration of *iso*pentyl alcohol by nitric acid in about 50—60% aqueous perchloric acid varies with acidity according to a form of J function.[6] Such evidence is generally accepted as indicating that a protonated species is being dehydrated in the rate-controlling portion of the mechanism. Strong indirect evidence in favour of Bonner and Frizel's thesis is afforded by the work summarised in the preceding paragraph, since it is inconceivable that the nitronium-ion mechanism could be responsible for both *C*- and *O*-nitration in aqueous nitric acid, with no added strong acid, and yet fail to take charge of *O*-nitration in the presence of a considerable concentration of perchloric acid.

In the experiments now described, various mono- and poly-hydric alcohols were nitrated with a constant excess of nitric acid in nitromethane, without or with initial additions of water or other solutes. As is usual in this laboratory, the kinetics were followed dilatometrically. We had become so accustomed to associating nitration with large contraction that the smallness of the volume changes accompanying *O*-nitration of alcohols was a surprise, though it should not have been since a nitro-group is only transferred from one oxygen atom to another and in the *O*-nitration of water there could be no volume change. In the *O*-nitration of methyl alcohol there is a contraction of only about 1/40 of that accompanying the *C*-nitration of toluene, and about 1/10 of that accompanying the *N*-nitration of *N*-methyl-2 : 4 : 6-trinitroaniline. Naturally, this involved our making dilatometers more sensitive by at least an order of magnitude than those used previously, and also a thermostat of similarly greater precision. Furthermore, a better method of setting up runs had to be adopted, and the previously inappreciable disturbances due to reaction heat, which now appeared prominently, had to be avoided. However, due care having been taken, the dilatometry of the small volume changes proved about as easy and accurate as that of the relatively large ones hitherto followed.

(*A*) *Conversion of Methyl Alcohol into Methyl Nitrate.*—(1) *Kinetic form: Effect of substrate concentration.* In initially dry nitromethane, with methyl alcohol concentrations not above 0·05M and nitric acid concentrations much larger but not above 2·5M, one obtains the typical volume–time curve of a zeroth-order nitration. After some initial irregularity while a steady temperature is being attained, a straight line of negative slope is traced,

[4] Bunton and Halevi, *J.*, 1952, 4917.
[5] Bunton, Halevi, and Llewellyn, *J.*, 1952, 4913.
[6] Bonner and Frizel, *Nature*, 1957, **179**, 1022.

XUM

which at a certain point turns sharply to one of zero slope. At this point the chemical reaction is over. The negative slope gives its zeroth-order rate-constant.

In other conditions, disturbances can be noticed. With substantially higher initial concentrations of methyl alcohol, *e.g.*, 0·1M or more, the downward-sloping part of the volume–time curve is not absolutely straight, its initial gradient being appreciably greater, *e.g.*, 10%, than its gradient over the latter part. The cause of this is not established, but it may be due to some kinetic solvent effect of the methyl alcohol (cf. sub-section *A*4, where it is shown that added water accelerates zeroth-order nitration).

As with all zeroth-order nitrations, the rate rises, as a steep function of the nitric acid concentration. A new disturbance arises if this concentration is increased above 3M to produce somewhat fast runs: a special kind of discontinuity then appears at the end of the downward-sloping branch of the volume–time curve. Instead of turning abruptly

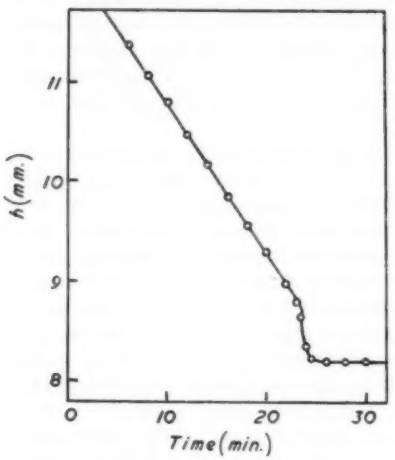


FIG. 1. *Volume–time curve in a nitration of methyl alcohol* (0·2M) *by nitric acid* (4M) *in nitromethane at* 25°. *The reaction is of zeroth order, and the short exponential segment of curve, here interposed between the usual two linear branches of the volume–time curve of such a reaction, is a cooling curve.*

horizontal, it turns, just as abruptly, to a much more steeply downward-sloping direction, and then, after a short exponential course, becomes horizontal (Fig. 1). This is regarded as a thermal effect, arising from dissipation of the heat of reaction. It is not seen in the less sensitive types of dilatometer, nor in the sensitive dilatometers unless the runs are fast. While nitration proceeds, heat is generated at a constant rate. During the first few minutes of a run, the dilatometer contents will attain a steady temperature such that the generated heat is lost to the thermostat at the same constant rate. When nitration abruptly stops, because no more methyl alcohol is left, the temperature of the dilatometer contents must fall to that of the thermostat. The resultant cooling-curve appears as the exponential contraction.

Apart from the disturbances mentioned, all runs on the nitration of methyl alcohol with a constant excess of nitric acid in initially dry nitromethane followed the zeroth-order

TABLE 1.—*Zeroth-order rate-constants* (k_0 *in moles* $l.^{-1}$ $sec.^{-1}$) *for the nitration of methyl alcohol by* 1·5M-*nitric acid in nitromethane at* 25°.

$[MeOH]_0$	0·0233	0·0236	0·0244	0·0356	0·0400	0·0524	0·0580	0·0653	0·0830
$10^5 k_0$	1·65	1·61	1·69	1·74	1·69	1·62	1·72	1·66	1·74

kinetic form with satisfactory precision. It is consistent that, within the same limitations, the zeroth-order rate-constants derived from different runs started with different concentrations of methyl alcohol, other conditions being the same, were identical (Table 1), the mean value of k_0 being $1{\cdot}68 \times 10^{-5}$ moles $l.^{-1}$ $sec.^{-1}$.

As the contents of a dilatometer did not provide enough material for satisfactory isolation of the nitration product, a larger-scale "dummy" kinetic run was conducted in a flask. Methyl nitrate was isolated from this and identified.

(2) *Rate comparison with aromatic nitration.* Since the mechanism of aromatic nitration is known, a comparison of the absolute rate of the zeroth-order nitration of methyl alcohol with the rate under the same conditions of the nitration of such aromatic compounds as follow the zeroth-order law provides important evidence concerning the mechanism of the *O*-nitration. That the zeroth-order rates are the same in the same conditions for the nitration of methyl alcohol, benzene, toluene, and ethylbenzene is shown in Table 2. These experiments on the hydrocarbons were carried out at the same time and with the same materials as those on methyl alcohol, in order to make the whole series comparable.

TABLE 2. *Zeroth-order rate-constants (k_0 in moles $l.^{-1}$ $sec.^{-1}$) for the nitration of methyl alcohol and of benzenoid hydrocarbons by 2·5M-nitric acid in nitromethane at 25°.*

	$[MeOH]_0$, As Table 1	$[C_6H_6]_0$, 0·110	$[Ph{\cdot}Me]_0$, 0·0748	$[Ph{\cdot}Et]_0$, 0·0675
10^5k_0	1·68 (mean)	1·72	1·70	1·66

(3) *Kinetic effects of acid, base, and salts.* The object of these experiments was to confirm the nitronium-ion mechanism with respect to step (1) of the mechanism, as expressed in scheme (I) of the preceding paper (p. 4358). It is expected that acids will accelerate reaction strongly, and neutral salts will do so mildly, but that bases will retard

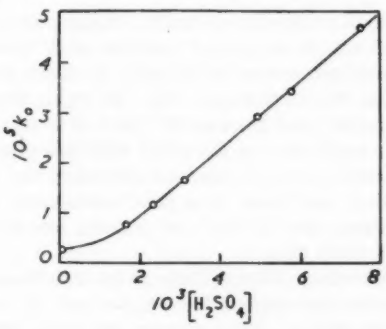


FIG. 2. *Effect of added sulphuric acid on the zeroth-order rate of nitration of methyl alcohol* (0·025M) *by nitric acid* (1·5M) *in nitromethane at* 25°.

reaction. The solvent throughout this group of experiments was initially dry nitromethane, and the nitration was in consequence of zeroth-order form, step (2) of scheme (I) being rate controlling. This kinetic form was preserved throughout these particular experiments, even under the retarding addition of a base.

The added acid was sulphuric acid, which is so much stronger than nitric acid that, even in somewhat low concentration, it wholly takes the place of that one of the two nitric acid molecules, written as the factors of step (1) in scheme I, which acts as proton-donor to the other. The observed zeroth-order rates are in Table 3. On the progressive addition of sulphuric acid, the accelerating effect is at first small but soon grows to its maximum. This can be understood because although the sulphuric acid protonates the nitric acid, this in turn will cause formed nitric acidium ion so to combine with original autoprotolytic nitrate ion that the ionic product of the nitric acid remains constant. Only when most of the pre-existing nitrate ion has been thus destroyed will the further addition of sulphuric acid produce its equivalent in an increased concentration of nitric acidium ion, and so will produce the linear increase, shown in Fig. 2, in the rate of formation of nitronium ion, and hence in rate of zeroth-order nitration.

As Table 3 shows, the addition of sodium perchlorate accelerates nitration. This is expected as a normal salt effect; for, according to the nitronium-ion mechanism, ions are being produced from neutral species in the kinetically significant part of the mechanism,

i.e., up to and including the rate-controlling step. Other salts are expected to act similarly, unless they exert superposed specific effects. Added potassium nitrate certainly does this, because it markedly retards nitration, as is also shown in Table 3. Although our figures are not extensive enough to permit a quantitative analysis of the superposed effects, the qualitative conclusion seems assured that the observed retarding effect is the net result of a normal-salt acceleration and a stronger specific retardation arising from the basic nature of the nitrate ion, which, as the lyate ion of the system, is the strongest base that can be introduced in quantity. According to the nitronium-ion mechanism, the nitrate ion must deprotonate such nitric acidium ion as is autoprotolytically formed in pre-equilibrium, and must thereby reduce the stationary concentration to which the rate of formation of nitronium ion, measured as zeroth-order nitration rate, is proportional.

TABLE 3. *Effects of added sulphuric acid, sodium perchlorate, and potassium nitrate on the zeroth-order rate-constants (k_0 in moles $l.^{-1}$ $sec.^{-1}$) of nitration of methyl alcohol (initially* 0·025 M*) by nitric acid in nitromethane at* 25°.

$[HNO_3]$ + $[H_2SO_4]$	0	0·00161	0·00231	0·00308	0·00492	0·00576	0·00744
= 1·5M, 10^5k_0	0·276	0·767	1·17	1·63	2·91	3·40	4·71
$[HNO_3]$ + $[NaClO_4]$	0	0·00231	0·00287	0·00409	0·00676		
= 2·5M, 10^5k_0	1·65	1·71	1·74	1·91	2·08		
$[HNO_3]$ + $[KNO_3]$	0	0·00131	0·00194	0·00297	0·00467	0·00538	0·00661
= 2·5M, 10^5k_0	1·65	1·30	1·19	1·05	0·99	0·98	0·88

(4) *Kinetic effect of water: change from zeroth to first order.* The object of these experiments was so to promote reversal of dehydration of the nitric acidium ion, that the formation of nitronium ion in step (2) of scheme (I) becomes included in the pre-equilibrium part of the mechanism, with the result that the nitronium ion is held in stationary concentration, and the rate at which it is removed by methyl alcohol becomes the nitration rate: our former zeroth-order will then give place to first-order kinetics. Once the change in kinetic order is fully accomplished the water, apart from any general medium effect which it may have as a polar co-solvent, should exert a specific retarding effect on the nitration, since it has now become one of the products of the extended pre-equilibrium [cf. scheme (I)].

The observations (Table 4) are as follows. Small or moderate initial additions of water have no detectable effect on the rate of zeroth-order nitrations started in otherwise dry nitromethane. By moderate, we mean amounts comparable with the amount of water produced in the nitration, and hence already much larger than the amounts of the acid, base, and salts which, in the preceding sub-sections, were shown to produce large kinetic effects. However, when water is added in quantities such as 0·1M which are substantially larger than those in which it is produced in the nitrations (0·025M) but still smaller than would make total water sufficiently competitive with the methyl alcohol to effect any large degree of re-hydration of formed nitronium ion, then, although the pre-equilibrium remains restricted to step (1) of scheme (I), and the zeroth-order form of nitration is accordingly preserved, the nitration is actually accelerated by the added water. Though this is contrary to one's preconceptions, *e.g.*, those based on descriptions in text-books of nitration, as to how water usually affects their rate, it can be understood as a general medium effect of water as a polar co-solvent; for in zeroth-order nitration, according to the nitronium-ion mechanism, ions, namely, nitronium and nitrate, are being produced from the neutral species, nitric acid molecules, in the kinetically significant part of the mechanism, namely steps (1) and (2) of scheme (I). Therefore, added water should accelerate zeroth-order nitration by its medium effect. However, when the water content is raised to 0·2M and above the rate begins to fall, and the reaction order in substrate simultaneously begins to rise from zero towards one, at first in the later part of the course of the reaction, but eventually throughout. At 0·8M-water the rate is still falling, but the reaction is practically completely converted into first-order form. Thereafter, if the concentration of water is

further increased, the first order rate-constant becomes steadily reduced; but now the kinetic form remains the same. We understand this as meaning that the co-solvent effect of water is less important than the specific retarding effect which water now acquires from having become included in the pre-equilibrium products of the combined stages (1) and (2), as rate-control is shifted from step (2) to step (3) of scheme (I), as happens when the kinetic order changes from zero to unity.

(5) *Mechanism of* O-*nitration.* Assuming that proton-loss from the conjugate acid of

TABLE 4. *Zeroth- and first-order rate-constants* (k_0 *in moles* $l.^{-1}$ $sec.^{-1}$ *and* k_1 *in* $sec.^{-1}$) *of nitration of methyl alcohol* (0·025M) *by nitric acid* (2·5M) *in nitromethane containing initially added water.*

$[H_2O]$ *	10^5k_0	Order	$[H_2O]$ *	10^5k_0	Order	$[H_2O]$ *	10^4k_0	Order
—	1·65	0	0·249	~1·9	~0	0·779	~11·9	~1
0·068	1·88	0	0·392	~1·7	impure	0·882	8·53	1
0·122	2·25	0	0·511	~1·6	impure	1·00	4·22	1
0·188	2·07	0				1·13	1·92	1

* *Added* water.

methyl nitrate would be rapid, in agreement with step (4) of scheme (I) (X = OMe), the preceding evidence satisfies all the critical kinetic requirements of that scheme. Thus the *O*-nitration of alcohols certainly proceeds by attack of pre-formed nitronium ion on non-bonding oxygen electrons of the alcohol.

(6) *Comparison of substrate reactivities in* C-, N-, *and* O-*nitration.* The rates of attack of nitronium ion on methyl alcohol and on toluene were compared by measuring first-order rate-constants for the nitration of methyl alcohol and of toluene in identical conditions in which both reactions follow first-order kinetics. At 25° in nitromethane containing 1·09M-water, the first-order constant for the nitration with 2·5M-nitric acid of methyl alcohol was $2·5 \times 10^{-4}$ $sec.^{-1}$, and of toluene was $2·0 \times 10^{-4}$ $sec.^{-1}$. If we take figures from the preceding paper (Section *A*6), in order to bring the *N*-nitration of *N*-methyl-2 : 4 : 6-trinitroaniline into comparison with the *O*-nitration of methyl alcohol and the *C*-nitration of simple aromatic hydrocarbons, we can set up the following scale of kinetic reactivities for nitronium ion of the unsaturated or unshared electrons of carbon, nitrogen, and oxygen in these substrates: Benzene, 1; *N*-methyl-2 : 4 : 6-trinitroaniline, 1·4; toluene, 24; methyl alcohol, 30. The corresponding figure for water probably lies between one and two orders of magnitude below that for benzene, and therefore about three orders below that for methyl alcohol.

(*B*) O-*Nitration of Other Mono- and Poly-hydric Alcohols.*—(1) p-*Nitrobenzyl alcohol.* The nitro-substituent in this compound serves the two purposes of preventing nitration in the aromatic ring, and reducing the tendency to oxidation in the side-chain. It is expected also, by its inductive effect, to reduce the reactivity of the unshared oxygen electrons towards nitronium ion.

However, the alcohol is readily nitrated by nitric acid in constant excess in initially dry nitromethane. The accompanying contraction is about the same as that applying in the nitration of methyl alcohol, a fact which itself is evidence that an *O*-nitration is under observation, as was confirmed by the isolation of *p*-nitrobenzyl nitrate.

The reaction is substantially of zeroth-order, although the volume–time graph remains strictly linear for only the first 90% of the total reaction and then undergoes some rounding as it runs into the horizontal branch representing completed reaction. This probably means that the intrinsic reactivity of the alcohol towards nitronium ion is only just high enough to permit the observation of zeroth-order kinetics. One observes the same thing in the nitration of benzene, though not in that of toluene or more reactive derivatives. It can be understood that, when the specific rate of reaction of the substrate with nitronium ion is, say, more than ten but less than a hundred times larger than the specific rate of the corresponding reaction of water, then, towards the end of reaction, when there is present

XUM

more than ten times as much water as there is of substrate, the water will have some success in its competition with the substrate for nitronium ion, which will no longer be captured wholly by the substrate; thus we find in this part of the reaction a departure from zeroth-order kinetics.

As shown in Table 5, the absolute rate of the zeroth-order nitration of *p*-nitrobenzyl alcohol is nearly the same as of methyl alcohol. The slightly smaller figure obtained for the nitro-alcohol may be simply a sign that, with this substance, we are near the lower limit of reactivity at which zeroth-order nitration can be observed.

TABLE 5. *Zeroth-order rate-constants (k_0 in moles l.$^{-1}$ sec.$^{-1}$) for the nitration of methyl and* p*-nitrobenzyl alcohols by nitric acid* (2·25M) *in nitromethane at* 25°.

Methyl alcohol	$[ROH]_0 = 0{\cdot}231$, $10^5k_0 = 1{\cdot}08$
p-Nitrobenzyl alcohol	$[ROH]_0 = 0{\cdot}400$, $10^5k_0 = 1{\cdot}00$

(2) neo*Pentyl alcohol.* In *O*-nitration, this alcohol is considerably less reactive than the other alcohols so far mentioned. In initially dry nitromethane, the nitration of *neo*-pentyl alcohol by nitric acid in constant excess shows a strong departure from zeroth-order form, and an absolute rate much below that of the zeroth-order nitrations. The kinetic order is not first, but between zeroth and first, approximating more closely to first on the whole, and especially in the later part of reaction.

The position of *neo*pentyl alcohol among the alcohols in *O*-nitration is comparable to that of chlorobenzene among benzene derivatives with respect to *C*-nitration. The nitration of chlorobenzene in nitromethane has the kinetic characteristics described in the preceding paragraph for the nitration of *neo*pentyl alcohol. We have made a rough comparison of the relative specific rates of reaction of *neo*pentyl alcohol and of chlorobenzene with nitronium ion, by comparing the first-order rate-constants that can be obtained for the nitration of either substrate with a constant excess of nitric acid in nitromethane containing small amounts of water. It appears that *neo*pentyl alcohol has a kinetic reactivity for nitronium ion about $\frac{3}{4}$ of that of chlorobenzene. It has been estimated, from experiments on competitive aromatic nitration, that the specific rate of reaction of chlorobenzene with nitronium ion is about 1/30 of that of the reaction of benzene. We might therefore extend the scale of reactivities for nitronium ion given at the end of the preceding section by assigning to *neo*pentyl alcohol a value about 1/40 of that of benzene, or 1/1200 of that of methyl alcohol.

(3) *Ethylene glycol.* The *O*-nitration with nitric acid in constant excess in initially dry nitromethane, follows a zeroth-order kinetic law, holding smoothly to the complete formation of the final product, ethylene dinitrate. The zeroth-order rate constant for overall conversion of the glycol is one-half of the constant applying to the nitration of methyl alcohol in identical conditions (Table 6).

This relation between the rate constants is natural, for it is implied in the kinetic form that the mononitration of the glycol and of its mononitrate occur at the same zeroth-order rate, *i.e.*, that the first and second hydroxyl groups in a glycol molecule take up nitronium ion independently of each other and just as fast, in each case, as nitronium ion becomes available. Therefore, in order to secure the complete conversion of a glycol molecule, we must wait for the formation of two nitronium ions, twice as long as we have to wait for such conversion of a methyl alcohol molecule; thus the rate is reduced to one-half.

(4) *Trimethylene glycol.* The same description applies. Zeroth-order rate-constants for the nitration of both glycols, and for glycerol, are included in Table 6.

TABLE 6. *Zeroth-order rate-constants (k_0 in moles l.$^{-1}$ sec.$^{-1}$) for the nitration of mono- and poly-hydric alcohols by* 2·5M*-nitric acid in nitromethane at* 25°.

	$[MeOH]_0$, 0·0244	$[C_2H_4(OH)_2]_0$, 0·0274	$[C_3H_6(OH)_2]_0$, 0·0169	$[C_3H_5(OH)_3]_0$, 0·0151
10^5k_0	1·69	0·83	0·84	0·88

(5) *Glycerol.* The *O*-nitration with nitric acid in constant excess in nitromethane passes through two kinetically well-separated phases, a zeroth-order succeeded by a first-order course. More particularly, the reaction proceeds to about two-thirds of its total extent at a constant rate almost equal to the rate of nitration of the glycols (cf. Table 6), after which the reaction is completed at a much reduced and exponentially diminishing rate.

Our interpretation is that two nitronium ions are trapped by the glycerol molecule as fast as they become available. Presumably they are taken up at the primary-alcoholic centres to form propan-2-ol 1 : 3-dinitrate. In this compound, the secondary alcoholic centre is relatively unreactive, and becomes the less successful competitor with water for formed nitronium ion, which it draws off only slowly from a stationary concentration, so accomplishing, with first-order kinetics, the last stage of esterification in the formation of glycerol trinitrate. First-order rate-constants for this last stage are given in Table 7. Although we have not directly compared rates, propan-2-ol 1 : 3-dinitrate appears to be considerably less reactive in first-order nitration than is *neo*pentyl alcohol.

TABLE 7. *First-order rate-constants (k_1 in sec.$^{-1}$) for the third step in the trinitration of glycerol by nitric acid in nitromethane at 25°.*

$[HNO_3]_0 = 4{\cdot}0$	$[\text{Glycerol}]_0 = 0{\cdot}168$	$10^4k_1 = 1{\cdot}36$	$[HNO_3]_0 = 5{\cdot}0$	$[\text{Glycerol}]_0 = 0{\cdot}062$	$10^4k_1 = 4{\cdot}50$

EXPERIMENTAL

Apparatus.—Owing to the smallness of the volume changes in *O*-nitration a particularly good thermostat as well as sensitive dilatometers were required.

The thermostat regulator contained, in two connected flat spirals of 1 cm. tubing, toluene sufficient to give a movement of mercury in the capillary of 1 metre per degree. The usual hot-wire switch having been found subject to a possible time-lag of several seconds, an electronic relay was constructed which worked very quickly, though it required frequent maintenance. The 25 W regulator-controlled heater supplemented a permanent heater so adjusted that it was just insufficient to maintain the temperature of 25°. Careful attention was paid to stirring and to thermal insulation of the 100-l. bath, particularly to insulation over the lid. In practice the temperature variation was about 0·0005°.

For aromatic nitrations, the ordinary tapless dilatometers of Benford and Ingold's type C [7] were used. For *O*-nitration, some tapless dilatometers were developed which had the required sensitivity, but also the disadvantage that they took about 15 min. to fill by suction through the fine capillary tube. Therefore we re-introduced taps (2 mm. vacuum) into our dilatometers of the types called " D " and " E ". Above a tap was a length of ordinary 2 mm. capillary tube attachable through a ball-and-socket joint to a capillary tube of similar diameter and an inverted U form, through which filling was accomplished. Below the tap, the dilatometer D contained a simple U of thin-walled quill tubing, 5 ml. in total capacity; and above the other limb of this U was a vertical length of 0·5 mm. precision-bore capillary tubing for the volume readings. The dilatometer E was identical with D except that the simple U of quill tubing was replaced by a helix of 20 ml. total capacity. Ordinary L grease was used for the taps, the attack on it by nitric acid being minimised by care in restricting it to the ground surface. Dilatometers were cleaned, and the grease was removed, after every run. The scale readings were made with a cathetometer, $\pm 0{\cdot}01$ mm. The constants of the dilatometers, *i.e.*, the fractional volume changes per unit scale length were as follows: C = 0·00195, D = 0·000190, E = 0·0000564 cm.$^{-1}$.

Procedure.—The empty dilatometer was placed in the thermostat. The nitric acid, just above its m. p., was weighed from a vacuum-jacketed pipette into nitromethane, just above its m. p., contained in a standard flask. This was placed in the thermostat and, after sufficient time for adjustment of the temperature, was made up to the mark with nitromethane. Meanwhile the organic substrate was weighed into 2 ml. of nitromethane in another weighed standard flask, thereby avoiding unaccounted loss by volatilisation when the substrate was methyl alcohol. This flask was now placed in the thermostat and allowed to attain its temperature. The nitric acid solution was now transferred to a small separating funnel above the other flask,

[7] Benford and Ingold, *J.*, 1938, 929.

XUM

and at once run into the latter, up to its mark, while the stop-watch was started. Then the reaction solution, well mixed, was sucked into the dilatometer, and the cathetometer readings were started.

Materials.—Methyl alcohol was purified by a standard method.[8] *p*-Nitrobenzyl alcohol, crystallised from water, had m. p. 92—93°. Ethane-1 : 2-diol, fractionated under low pressure, had n_D^{25} 1·4300. Similarly distilled propane-1 : 3-diol had n_D^{25} 1·4384, and glycerol n_D^{25} 1·4725. Purification of nitric acid and of nitromethane is described in the preceding paper.

Products.—Methyl nitrate was isolated as follows. The nitromethane solution in which methyl alcohol had been nitrated was washed with small volumes of ice-cold water and ice-cold saturated aqueous sodium chloride, and was then neutralised with sodium hydrogen carbonate, filtered, and dried ($MgSO_4$). The filtered solution was fractionated at 12 mm. pressure through a 30 cm. packed column, and the methyl nitrate was trapped at −80° and redistilled at a similar pressure. It gave a strong positive test for nitrate and a negative one for nitrite (n_D^{25} 1·3720; Found: C, 15·8; H, 4·2. Calc. for CH_3O_3N: C, 15·6; H, 3·9%). *p*-Nitrobenzyl nitrate, recovered by crystallisation after a nitration, had m. p. 67—68° (Found: C, 42·6; H, 3·4. Calc. for $C_6H_4O_5N_2$: C, 42·4; H, 3·0%).

We gratefully acknowledge the exploratory work of Dr. A. J. Kresge.

William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1. [*Received, July 25th*, 1958.]

[8] Vogel, " Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p. 169.

---

886. *Reactions of Tin*(IV) *Halides with Ammonia Derivatives. Part II.*[1] *The Reaction of Liquid Ammonia with Tin*(IV) *Bromide, Diammonium Hexabromostannate*(IV), *and Tin*(IV) *Iodide.*

By E. Bannister and G. W. A. Fowles.

The reaction between liquid ammonia and tin(IV) bromide or diammonium hexabromostannate(IV) gives ammonium bromide and the ammonobasic tin(IV) bromide, $SnBr(NH_2)_3$. Liquid ammonia and tin(IV) iodide react to give ammonium iodide and the ammonobasic tin(IV) iodide, $SnI_2(NH_2)_2$, but on washing with liquid ammonia further solvolysis occurs and $SnI(NH_2)_3$ can be isolated. The thermal decomposition of these substances has been examined.

The vapour pressures of ammonia adducts formed by ammonium bromide and ammonium iodide have been measured over a wide temperature range.

Our study of the reaction of tin(IV) chloride [1] with liquid ammonia has now been extended to the analogous reactions of tin(IV) bromide and tin(IV) iodide. These reactions have previously received little attention, and with tin(IV) bromide, for instance, there is only an early report [2] of the formation of a diammine. With the tin(IV) iodide–ammonia system [3,4,5] work has been restricted to passing ammonia gas through solutions of the iodide in various organic solvents, and the isolation of compounds with overall formulæ SnI_4,xNH_3, where $x = 3$, 4, 6, and 8. No structure has been formulated for these compounds, which are probably mixtures of ammonolysis products, particularly in view of the formation [4] of unstable higher ammonia adducts; these could well be those ammonia adducts formed by the ammonium iodide produced on ammonolysis.

The systems formed by ammonia with tin(IV) bromide, diammonium hexabromostannate(IV), tin(IV) iodide, ammonium bromide, and ammonium iodide have been examined tensimetrically. In addition, the normal liquid-ammonia extraction procedure has been used to obtain ammonolysis products free from ammonium halides.

[1] Part I, Bannister and Fowles, *J.*, 1958, 751.
[2] Rayman and Preis, *Annalen*, 1884, **223**, 326.
[3] Personne, *Compt. rend.*, 1862, **54**, 216.
[4] Ephraim and Schmidt, *Ber.*, 1909, **42**, 3856.
[5] Cooper and Wardlaw, *J.*, 1930, 1141.

Experimental

Materials.—Tin(IV) bromide (British Drug Houses) was distilled *in vacuo* and condensed into suitable containers.[6] Tin(IV) iodide (British Drug Houses) was recrystallised from anhydrous chloroform and stored *in vacuo*. Ammonia was purified as previously described.[1] Ammonium bromide and ammonium iodide (Hopkin and Williams) were recrystallised from doubly-distilled water and dried at 60° *in vacuo* for several hours before use.

Diammonium hexabromostannate(IV) was prepared by mixing concentrated solutions of ammonium bromide and tin(IV) bromide in 30% hydrobromic acid, the yellow precipitate being washed with ice-cold hydrobromic acid and dried (NaOH) [Found: Br, 75·6; N, 4·4. Calc. for $(NH_4)_2SnBr_6$: Br, 75·6; N, 4·4%]. Analogous attempts to make the corresponding diammonium and dirubidium hexaiodostannates(IV) reasonably pure were unsuccessful.

Analysis.—Tin and nitrogen were determined as described previously.[1] Bromine was determined by potentiometric titration with silver nitrate solution, and iodine by titration with potassium iodate in hydrochloric acid solution. Where products were difficult to remove from the reaction vessel, they were hydrolysed *in situ*; a ratio is then quoted.

Reactions and Tensimetric Studies.—These were carried out in a closed vacuum system similar to that used in Part I.

(i) *The ammonium bromide–ammonia and ammonium iodide–ammonia systems.* The pressure–composition isotherms obtained at −36° agree with those obtained by Watt and McBride [7] at −35·5°; they accordingly confirm the existence of the ammonia adducts NH_4Br,xNH_3, with $x = 1·5$ and 3, and NH_4I,yNH_3, with $y = 1$, 2, 3, and 4. The same adducts appeared to be formed at −63°, but because of their low dissociation pressures it was not possible clearly to distinguish between $NH_4I,2NH_3$ and NH_4I,NH_3. Since the equilibrium dissociation pressures were to be used diagnostically in the tin(IV) halide–ammonia systems, they were measured [8] over a fairly wide temperature range. Each equilibrium was clearly established at −36°, and then the temperature was varied and the equilibrium pressure of ammonia determined. The results, expressed as equations, are given in Table 1.

Table 1. *Equilibrium pressures in the ammonium bromide–ammonia and ammonium iodide–ammonia systems.*

Equilibrium	$\log_{10} P_{mm} = (-a/T) + b$ a	b	Temp. range	$-\Delta H$ (kcal./mole)
$NH_4Br,3NH_3 \rightleftharpoons NH_4Br,1·5NH_3 + 1·5NH_3$	2001·7	10·0844	− 64·5° to 0·0°	9·16
$NH_4Br,1·5NH_3 \longleftarrow NH_4Br + 1·5NH_3$	1866·4	9·3852	−64·5 to 0·0	8·54
$NH_4I,4NH_3 \rightleftharpoons NH_4I,3NH_3 + NH_3$	1970·1	10·0088	−62·3 to −17·8	9·02
$NH_4I,3NH_3 \rightleftharpoons NH_4I,2NH_3 + NH_3$	1753·3	8·9530	−60·3 to −23·0	8·02
$NH_4I,2NH_3 \rightleftharpoons NH_4I,NH_3 + NH_3$	2125·5	10·2024	−54·3 to 0·0	9·73
$NH_4I,NH_3 \rightleftharpoons NH_4I + NH_3$	2168·9	9·6922	−39·8 to 22·8	9·93

(ii) *Tin*(IV) *bromide–ammonia and tin*(IV) *iodide–ammonia reactions. Washing procedure.* After extensive washing of tin(IV) bromide with liquid ammonia (25 × 50 ml.) to remove ammonium bromide, a white solid remained undissolved (Found: Sn : Br : N = 1·00 : 0·95 : 3·05). It was allowed to come into contact with excess of ammonia and a pressure–composition isotherm was obtained, from which it appeared to contain no free ammonium bromide, although it did form simple ammonia adducts; these appeared to be a mono- and probably a di-adduct [cf. Fig. 1(*a*)] although it is difficult to establish these precisely because of their low dissociation pressures. The portion soluble in liquid ammonia (Found Sn : Br : N = 1·00 : 18·05 : 17·90) was mainly ammonium bromide.

With tin(IV) iodide, the white product initially formed was relatively soluble in liquid ammonia, and had entirely dissolved after about 15 washes. The residue after only 5 washes, which became pale yellow on pumping, had Sn : I : N = 1·00 : 1·30 : 3·30, but after a further

[6] Fowles and Pleass, *J. Chem. Educ.*, 1956, **33**, 640.
[7] Watt and McBride, *J. Amer. Chem. Soc.*, 1955, **77**, 1317.
[8] Fowles and Pollard, *J.*, 1952, 4938.

XUM

5 washes 1·00 : 1·01 : 2·99. The soluble portion after ten washes had Sn : I : N = 1·00 : 4·43 : 6·60. It seems, therefore, that the soluble portion has an overall composition $SnI_4,6NH_3$, corresponding to a mixture $SnI(NH_2)_3 + 3NH_4I$, but that a little excess of ammonium iodide is present, in agreement with the insoluble tin compound with Sn : I < 1 : 4.

The ammonobasic tin(IV) iodide, $SnI(NH_2)_3$, was fairly stable *in vacuo* up to 100°, but on

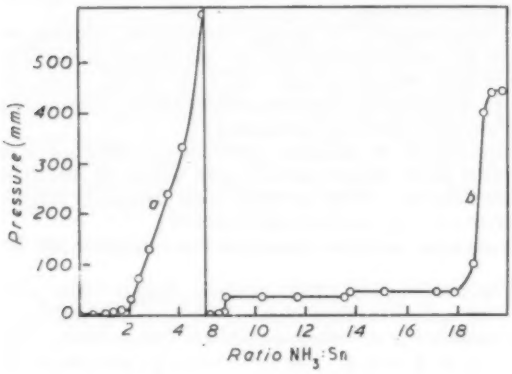


FIG. 1. *Tensimetry of* (*a*) $SnBr(NH_2)_3$ *and* (*b*) $SnBr_4$.

FIG. 2. *Tensimetry of* (*a*) SnI_4 *and* (*b*) $(NH_4)_2SnBr_6$.

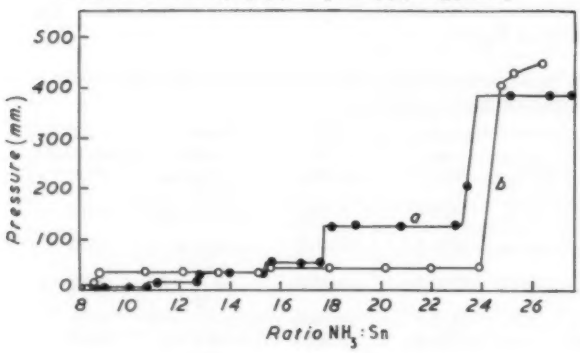
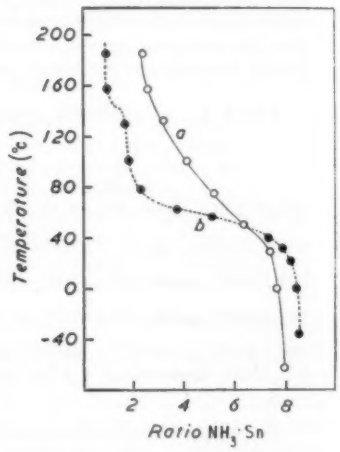


FIG. 3. *Tensimetry of* (*a*) $SnBr_4$ *and* (*b*) SnI_4.



heating to 180° lost 2 mol. of ammonia and formed an orange-red sublimate. The unsublimed rust-coloured residue reacted vigorously with dilute sulphuric acid, and completely dissolved in concentrated hydrochloric acid (Found: Sn : I : N = 1·00 : 0·77 : 1·05).

Tensimetry at −36° *and* −63°.—The isotherms at −36° for the tin(IV) bromide–ammonia and the tin(IV) iodide–ammonia system are shown in Figs. 1(*b*) and 2(*a*) respectively; the −63° isotherms were very similar in general appearance, except that the univariant steps in the tin(IV) bromide–ammonia system were approximately 10% shorter. After removal of excess of ammonia, the materials remaining had overall compositions $SnX_4,8NH_3$; the results of the progressive thermal decomposition of these substances are shown in Figs. 3(*a*) and 3(*b*).

With $SnBr_4,8NH_3$, a *sublimate* started to form at 130° and by 180° almost all had sublimed into the cooler part of the tube (Found: Br, 66·3; N, 5·91. $SnBr_4,2NH_3$ requires Br, 67·7; N, 5·93%). With $SnI_4,8NH_3$, the decomposition was more complex, and at least two different sublimates were formed. Around 30° a dark red one was formed, but above 60° a yellow one,

which gradually darkened on further heating. The unsublimed residue remaining at 180°, which contained about one-fifth of the tin originally used [as tin(IV) iodide] and had strong reducing properties in hydrochloric acid solution (Found Sn : I : N = 1·0 : 2·1 : 0·2), appears to be largely tin(II) iodide.

The isotherm obtained for the diammonium hexabromostannate(IV)–ammonia system at −36° is shown in Fig. 2(*b*). After removal of excess of ammonia at −36°, the solid remaining had an overall composition $(NH_4)_2SnBr_6,8NH_3$; the progressive thermal decomposition of this solid closely resembled that of $SnBr_4,8NH_3$ in that a sublimate of $SnBr_4,2NH_3$ was formed (Found: Sn : Br : N = 1·00 : 3·98 : 1·99); a residue of ammonium bromide remained at 180°.

Discussion

In Part I we discussed the reaction of tin(IV) chloride with ammonia, and concluded that after initial co-ordination of an ammonia molecule, hydrogen chloride was eliminated, leaving as the final product a mixture of the ammonobasic tin(IV) chloride, $SnCl(NH_2)_3$, and ammonium chloride.

$$SnCl_4 + 2NH_3 \rightleftharpoons SnCl_3NH_2 + NH_4Cl$$
$$SnCl_3NH_2 + 2NH_3 \rightleftharpoons SnCl_2(NH_2)_2 + NH_4Cl$$
$$SnCl_2(NH_2)_2 + 2NH_3 \rightleftharpoons SnCl(NH_2)_3 + NH_4Cl$$

The pure ammonobasic tin(IV) chloride was obtained by washing out the soluble ammonium chloride with liquid ammonia. Now tin(IV) bromide and iodide should be ammonolysed analogously, except that the ammonolysis might go even further in view of the weaker tin–bromine and tin–iodine bonds. Our experiments show, however, that when the soluble ammonium halide is leached with liquid ammonia, the ammonolysis products remaining are analogous to that obtained with tin(IV) chloride; thus the ammonobasic tin(IV) halides, $SnBr(NH_2)_3$ and $SnI(NH_2)_3$, have been isolated. All the ammonobasic tin(IV) halides show some solubility in liquid ammonia, particularly the iodide. They are even more soluble in the presence of ammonium halides, and we attribute this to the formation of complex anionic tin species. Since the ammonobasic tin(IV) bromide, $SnBr(NH_2)_3$, forms ammonia adducts, its relatively poor acceptor properties are evidently not the reason for the last tin–bromine bond's not being ammonolysed. In view of the tendency for many tetrahalides to form compounds of the general formula $MX(NH_2)_3$, *e.g.*, with tin(IV) chloride, titanium(IV) chloride,[9] bromide,[10] and iodide,[10] and vanadium(IV) chloride,[11] it seems that the last halogen atom is particularly difficult to replace. Complete ammonolysis could, no doubt, be effected under more "alkaline" conditions, *i.e.*, with potassium amide, since early work by Fitzgerald[12] indicated that potassium amide in liquid ammonia completely replaced iodine atoms in tin(IV) iodide.

The thermal decomposition of the ammonobasic tin(IV) iodide appears to be analogous to that of the corresponding chloride,[13] the main reaction being $SnI(NH_2)_3 \longrightarrow SnIN + 2NH_3$. Side reactions such as $4SnIN \longrightarrow Sn_3N_4 + SnI_4$ evidently occur, however, and it is probable that the orange-red sublimate formed on heating to 180° is a mixture of tin(IV) iodide and its diammine.

Before considering the tensimetric results, we recall that although the ammonolysis of tin(IV) chloride at −63° gave a mixture of the ammonobasic tin(IV) chloride and ammonium chloride, $[SnCl(NH_2)_3 + 3NH_4Cl]$, 2 mol. of ammonium chloride could no longer be detected on raising the temperature to −36°. This was attributed to the formation of a complex, $[NH_4]_2[SnCl_3(NH_2)_3]$, which remained as a stable single phase in the solid state, so that the ammonium chloride could not be detected through the formation of its characteristic ammonia triadduct. Although tin(IV) bromide and tin(IV) iodide

[9] Fowles and Pollard, *J.*, 1953, 2588.
[10] Fowles and Nicholls, unpublished observations.
[11] Fowles and Nicholls, *J.*, 1958, 1687.
[12] Fitzgerald, *J. Amer. Chem. Soc.*, 1907, **29**, 1693.
[13] Schwarz and Jeanmaire, *Ber.*, 1932, **65**, 1443.

resemble the chloride in giving analogous products in the washing experiments, [$SnBr(NH_2)_3$ and $SnI(NH_2)_3$], their tensimetric properties differ. With neither halide, for instance, does an increase in temperature appreciably alter the amount of ammonium halide found; at $-63°$ and $-36°$ 3 mol. of ammonium bromide and 2 of ammonium iodide can be detected in the appropriate tin(IV) halide–ammonia system. It seems that in the tin(IV) bromide–ammonia system any complex formed is unstable in the solid state. Thus 3 mol. of ammonium bromide are detected, and the product has an overall composition $SnBr_4,8NH_3$, so that the reaction at $-36°$ must be $SnBr_4 + 8NH_3 \longrightarrow SnBr(NH_2)_3,2NH_3 + 3NH_4Br$. As we might expect, ammonolysis is not quite as extensive at $-63°$, and only 2·7 mol. of ammonium bromide are found. Moreover, the reaction cannot be

$$SnBr_4 + 8NH_3 \longrightarrow Sn(NH_2)_4 + 4NH_4Br \longrightarrow [NH_4][SnBr(NH_2)_4] + 3NH_4Br$$

because the amide is not formed even in the washing experiments, where conditions are much more favourable for maximum ammonolysis.

Further evidence for the non-formation of a stable complex is provided by the tensimetry of the diammonium hexabromostannate(IV)–ammonia system, where 5 mol. of ammonium bromide can be detected and the final product has an overall composition $(NH_4)_2SnBr_6,8NH_3$. In liquid ammonia the complex salt evidently behaves as a mixture of ammonium bromide and tin(IV) bromide, *i.e.*,

$$(NH_4)_2SnBr_6 \longrightarrow 2NH_4Br + SnBr_4 \xrightarrow{NH_3} 5NH_4Br + SnBr(NH_2)_3,2NH_3$$

The alternative explanation, a direct ammonolysis of five tin–bromine bonds in the anion, is ruled out because the final product would have an overall composition $(NH_4)_2SnBr_6,10NH_3$ {*i.e.* $[NH_4]_2[SnBr(NH_2)_5] + 5NH_4Br$}. Moreover, on thermal decomposition, the products of the reaction of ammonia with tin(IV) bromide and diammonium hexabromostannate(IV) behave very similarly:

$$SnBr_4,8NH_3 \longrightarrow SnBr_4,2NH_3 \text{ at } 180°;\ (NH_4)_2SnBr_6,8NH_3 \longrightarrow SnBr_4,2NH_3 \text{ at } 180°$$

A sublimate of the diammine of tin(IV) bromide is formed in each case, but a residue of ammonium bromide remains, as would be expected from the decomposition of the product formed by the complex salt. In view of its volatility, the diammine of tin(IV) bromide is evidently a simple addition compound [similar to that formed by tin(IV) chloride] in which the tin atom achieves a covalency of six ($5s5p^35d^2$).

With tin(IV) iodide, only 2 mol. of ammonium iodide can be detected, even though three tin–iodine bonds can be ammonolysed in the washing experiments. In view of the results of the tin(IV) bromine–ammonia reaction, it is unlikely that formation of a stable complex can account for the " missing " mol. of ammonium iodide, particularly since the complex tin anions decrease in stability along the series $[SnCl_6]^{2-}$, $[SnBr_6]^{2-}$, $[SnI_6]^{2-}$. Under the conditions of the tensimetric studies, tin(IV) iodide is probably less ammonolysed than either of the other two halides. This may arise from the high solubility of ammonium iodide in liquid ammonia, leading to very acid conditions when tin(IV) iodide is ammonolysed with only a slight excess of ammonia. Under these conditions, the reaction would proceed only as far as the replacement of two iodine atoms by amino-groups: $SnI_4 + 8NH_3 \longrightarrow SnI_2(NH_2)_2,4NH_3 + 2NH_4I$.

The thermal decomposition of the reaction mixture is evidently quite complex, but in view of the residue of tin(II) iodide at 180° it seems that at least some of the product is reduced, with the liberation of iodine.

We thank the International Tin Research Council for a maintenance grant (to E. B.).

THE UNIVERSITY, SOUTHAMPTON. [*Received, August 8th*, 1958.]

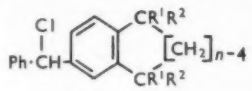
887. *Relation between Hyperconjugation and Conformation. Part III.* Ethyl Alcoholysis of Some Derivatives of Diphenylmethyl Chloride.*

By G. Baddeley and M. Gordon.

Derivatives (II, $n = 5$, 6, and 7) and (III, $n = 5$ and 6) have been prepared and their reactivities in ethanolysis measured and compared with those for the chlorides (I, $n = 5$, 6, and 7). The comparison affords evidence for the view [1] that hyperconjugation of methylene and phenyl groups varies with change in the conformational relationship of the groups.

The reactivities of 4-*cyclo*pentyl-, 4-*cyclo*hexyl-, and 4-*iso*propyl-diphenylmethyl chloride in ethanolysis decrease in this order.

Rates of unimolecular solvolysis of the chlorides (I; $n = 5$, 6, and 7) decrease in this order and have been offered [2] as evidence for the view [1] that hyperconjugation of methylene group and aromatic ring in the system $Ar\overset{\alpha}{C}H_2\overset{\beta}{C}<$ decreases progressively as the β-carbon atom lies at increasing distances from the plane of the ring. According to this interpretation, should one or both of the hydrogen atoms of the α-methylene group be replaced by methyl as in the chlorides (II and III; $n = 5$, 6, and 7) the reactivities of the chlorides should depend less on the value of n. In fact, the contribution by hyperconjugation to the reactivities of the chlorides (III), though not zero since it is generally accepted that the C–C bond can hyperconjugate though to a less extent than the C–H bond, should not be altered by change in the value of n. This follows from the assumption that the *tert.*-butyl group resembles the methyl group in having its hyperconjugative effect unaffected by rotation of the group about the bond joining it to the benzene ring. We have prepared the chlorides (II; $n = 5$, 6, and 7) and (III; $n = 5$ and 6); the kinetic data for their solvolysis in dry ethyl alcohol are assembled in Table 1 together with those previously reported for the chlorides (I; $n = 5$, 6, and 7). Table 2 provides a comparison of the relative rates of solvolysis at 0° for each series of chlorides.



(I ; $R^1 = R^2 = H$)
(II ; $R^1 = H$; $R^2 = Me$)
(III ; $R^1 = R^2 = Me$)

Table 1. *Arrhenius parameters for the formation of hydrogen chloride by the ethanolysis of the chlorides.*

Chloride	At 0·0° 10^5k (sec.$^{-1}$)	At 20·0° 10^5k (sec.$^{-1}$)	E (kcal./mole)	$10^{-10}A$ (sec.$^{-1}$)	Chloride	At 0·0° 10^5k (sec.$^{-1}$)	At 20·0° 10^5k (sec.$^{-1}$)	E (kcal./mole)	$10^{-10}A$ (sec.$^{-1}$)
I; $n = 5$ ...	23·3	205	17·3	1·5	II; $n = 5$	14·8	160	18·9	15·8
$n = 6$ ...	17·9	172	17·9	1·7	$n = 6$	11·9	130	19·1	15·5
$n = 7$ ...	15·1	147	18·0	2·0	$n = 7$	12·1	142	19·4	15·8
					III; $n = 5$	10·9	123	19·2	25·1
					$n = 6$	9·6	113	19·6	37·4

2-Phenylmethyl chlorides	At 0·0° 10^5k (sec.$^{-1}$)	At 20·0° 10^5k (sec.$^{-1}$)	At 25·0° 10^5k (sec.$^{-1}$)	E (kcal./mole	$10^{-10}A$ (sec.$^{-1}$)
4-*cyclo*Pentyl-	7·51	82·9	144	19·1	11·6
4-*cyclo*Hexyl-	5·75	67·9	122	19·3	13·8
4-*iso*Propyl- [3]	—	—	106	—	—

As expected, change in reactivity is greatest in series (I) and least in (III); thus the data provide evidence for the view that hyperconjugation of methylene and phenyl groups

* Part II, *J.*, 1958, 3171.

[1] Baddeley, Chadwick, and Rawlinson, *Nature*, 1949, **164**, 833; Baddeley and Gordon, *J.*, 1952, 2190.

[2] Arnold and Truett, *J. Amer. Chem. Soc.*, 1951, **73**, 5508.

[3] Hughes, Ingold, and Taher, *J.*, 1940, 949.

XUM

is altered by change in the conformational relationship of the groups. It is noteworthy that whereas the contribution of hyperconjugation to the reactivity of (III; $n = 6$) is expected to be about the same as that to the reactivity of (III; $n = 5$), these compounds have different reactivities. It follows, therefore, that the differences in reactivity between members of the series of chlorides (I) and (II) cannot be attributed wholly to differences in hyperconjugation.

TABLE 2. *Relative rates of ethanolysis at 0·0° for each of the series of chlorides, (I), (II), and (III).*

	(I)	(II)	(III)
$n = 5$	100	100	100
$n = 6$	77	80	88
$n = 7$	65	82	—

The reactivity of 4-*cyclo*pentyldiphenylmethyl chloride is greater than that of the corresponding *cyclo*hexyl derivative (see Table 1) as expected since the *cyclo*pentyl group holds its α-methylene group away from the *ortho*-positions of the benzene ring and so diminishes steric interaction. This effect of the five-membered ring has been observed in other instances. However, other effects, such as the greater aptitude of the *cyclo*pentyl group to provide an exocyclic double bond, may contribute to the difference in reactivity.

EXPERIMENTAL

Materials.—Hydrocarbons. *iso*Propyl-, *cyclo*pentyl-, and *cyclo*hexyl-benzene were prepared by previously described methods. 1 : 3-Dimethylindane, b. p. 199—201°, was obtained by catalytic hydrogenation of 1 : 3-dimethylindene,[4] the product of distillation of 1 : 3-dimethylindan-1-ol at atmospheric pressure. 1 : 2 : 3 : 4-Tetrahydro-1 : 4-dimethylnaphthalene, b. p. 104—105°/12 mm., was given by hydrogenation of 1 : 2-dihydro-1 : 4-dimethylnaphthalene,[5] the product of dehydration of 1 : 2 : 3 : 4-tetrahydro-1-hydroxy-1 : 4-dimethylnaphthalene with formic acid. 5-Phenylhexanoyl chloride, b. p. 145—147°/16 mm., was obtained from the acid [6] by the action of thionyl chloride, and gave 3-methyl-1 : 2-benzo*cyclo*hepten-7-one, b. p. 148—150°/16 mm., *semicarbazone*, m. p. 204—205° (Found: C, 68·1; H, 7·5; N, 17·7. $C_{13}H_{17}ON_3$ requires C, 67·5; H, 7·4; N, 18·2%), when cyclised with aluminium chloride as described by Baker and Aspinall.[7] This ketone afforded 3 : 7-dimethyl-1 : 2-benzo*cyclo*hepten-3-ol which gave 3 : 7-*dimethyl*-1 : 2-*benzo*cyclo*hepta*-1 : 3-*diene*, b. p. 123—124°/17 mm. (Found: C, 90·5; H, 9·4. $C_{13}H_{16}$ requires C, 90·7; H, 9·3%). 3 : 7-*Dimethylbenzo*cyclo*heptene*, b. p. 121—123°/18 mm. (Found: C, 90·0; H, 10·0. $C_{13}H_{18}$ requires C, 89·7; H, 10·3%), was obtained by catalytic hydrogenation. 1 : 1 : 3 : 3-Tetramethylindane,[8] b. p. 208—210°, was readily afforded by the action of 85% sulphuric acid on 2 : 5-dimethyl-4-phenylpentan-2-ol or the olefin obtained from it by the action of formic acid.

1 : 2 : 3 : 4-Tetrahydro-1 : 1 : 4 : 4-tetramethylnaphthalene,[9] b. p. 248°/760 mm., was given by the interaction of 2 : 5-dichloro-2 : 5-dimethylhexane (the product of interaction of the corresponding diol, m. p. 88—89°, and hydrogen chloride), benzene, and aluminium chloride. The preparation of *cyclo*hexylbenzene,[10] b. p. 239°/760 mm., involved 1-phenyl*cyclo*hexanol and 1-phenyl*cyclo*hexane as intermediates. *cyclo*Pentylbenzene, b. p. 216—217°/760 mm., was similarly obtained.

Ketones. Aluminium chloride (1·5 mol.) was covered with redistilled ethylene dichloride and benzoyl chloride (1·25 mol.) was gradually added together with sufficient ethylene dichloride to keep the acid chloride–aluminium chloride complex in solution. The solution was decanted on the appropriate aromatic hydrocarbon, and after being kept overnight the mixture was

[4] von Braun and Kirschbaum, *Ber.*, 1913, **46**, 3041.
[5] Kloetzel, *J. Amer. Chem. Soc.*, 1940, **62**, 1710.
[6] Nenitzescu and Gavat, *Annalen*, 1935, **519**, 271.
[7] *J.*, 1950, 745.
[8] Bogert and Davidson, *J. Amer. Chem. Soc.*, 1934, **56**, 187.
[9] Bruson and Kroeger, *ibid.*, 1940, **62**, 36.
[10] Sabatier and Murat, *Compt. rend.*, 1912, **154**, 1390.

poured on ice and hydrochloric acid. The organic layer was separated, dried (K_2CO_3), and distilled.

The following derivatives of benzophenone were obtained: 3 : 4-(3 : 5-dimethyl*cyclo*penteno)-, 204—205°/0·25 mm. (Found: C, 86·5; H, 7·1. Calc. for $C_{18}H_{18}O$: C, 86·4; H, 7·2%); 3 : 4-(3 : 6-dimethyl*cyclo*hexeno)-, b. p. 205—206°/0·25 mm. (Found: C, 86·2; H, 7·5. Calc. for $C_{19}H_{20}O$: C, 86·4; H, 7·6%); 3 : 4-(3 : 7-dimethyl*cyclo*hepteno)-, b. p. 198°/0·07 mm. (Found: C, 86·5; H, 8·0. Calc. for $C_{20}H_{22}O$: C, 86·3; H, 7·9%); 3 : 4-(3 : 3 : 5 : 5-*tetramethyl*cyclo*penteno*)-, b. p. 190°/0·5 mm., needles, m. p. 70—71° from ethanol (Found: C, 85·9; H, 7·9. $C_{20}H_{22}O$ requires C, 86·3; H, 7·9%); 3 : 4-(3 : 3 : 6 : 6-*tetramethyl*cyclo*hexeno*)-, b. p. 196—198°/0·3 mm., needles, m. p. 77—78° from ethanol (Found: C, 86·2; H, 8·3. $C_{21}H_{24}O$ requires C, 86·3; H, 8·2%); 4-*cyclo*pentyl-, b. p. 175—177°/0·06 mm. (Found: C, 86·1; H, 7·4. Calc. for $C_{18}H_{18}O$: C, 86·4; H, 7·2%); 4-*cyclo*hexyl-,[11] b. p. 197—199°/0·12 mm. (Found: C, 86·2; H, 7·4. Calc. for $C_{19}H_{20}O$: C, 86·4; H, 7·6%).

Alcohols. The following derivatives of diphenylmethanol were obtained from the corresponding benzophenones by reduction with lithium aluminium hydride or with zinc dust and alkali;[3] 3 : 4-(3 : 5-*dimethyl*cyclo*penteno*)-, b. p. 213—215°/13 mm., needles, m. p. 62·5—63·5° from light petroleum (Found: C, 85·5; H, 7·8. $C_{18}H_{20}O$ requires C, 85·7; H, 7·9%); 3 : 4-(3 : 6-dimethyl*cyclo*hexeno)-, b. p. 189—191°/0·1 mm. (Found: C, 85·5; H, 8·5. Calc. for $C_{19}H_{22}O$: C, 85·7; H, 8·3%); 3 : 4-(3 : 7-dimethyl*cyclo*hepteno)-, b. p. 190—192°/0·07 mm. (Found: C, 85·4; H, 8·6. Calc. for $C_{20}H_{24}O$: C, 85·7; H, 8·6%); 3 : 4-(3 : 3 : 5 : 5-*tetramethyl*cyclo*penteno*)-, needles, m. p. 118—119° from light petroleum (Found: C, 84·9; H, 9·0. $C_{21}H_{24}O$ requires C, 85·7; H, 8·9%); 4-cyclo*pentyl*-, needles, m. p. 52—53° from light petroleum (Found: C, 85·9; H, 8·1. $C_{18}H_{20}O$ requires C, 85·7; H, 7·9%); 4-cyclo*hexyl*-, needles, m. p. 53—54° (Found: C, 85·8; H, 8·7. $C_{19}H_{22}O$ requires C, 85·7; H, 8·3%).

Chlorides. The following derivatives of diphenylmethyl chloride were prepared by passing dry hydrogen chloride for 24 hours into a solution or suspension of the corresponding alcohols in light petroleum (b. p. 60—80°). The petroleum was then decanted from a lower aqueous layer and dried ($CaCl_2$); the solvent was removed under reduced pressure and in the absence of moisture and oxygen and the residue was rapidly distilled at 0·1 mm., using a preheated oil-bath. In all instances, the chloride before and after distillation provided rates of ethanolysis which, for a given temperature, did not differ by more than 2%. The approximate b. p.s were: 3 : 4-(dimethyl*cyclo*penteno)-, b. p. 170° (Found: Cl, 13·1. Calc. for $C_{18}H_{19}Cl$: Cl, 13·1%); 3 : 4-(3 : 6-dimethyl*cyclo*hexeno)-, b. p. 175° (Found: Cl, 12·3. Calc. for $C_{19}H_{21}Cl$: Cl, 12·5%); 3 : 4-(3 : 7-dimethyl*cyclo*hepteno)-, b. p. 180° (Found: Cl, 11·8. Calc. for $C_{20}H_{23}Cl$: Cl, 11·9%); 3 : 4-(3 : 3 : 5 : 5-tetramethyl*cyclo*penteno)-, b. p. 180° (Found: Cl, 11·6. Calc. for $C_{20}H_{23}Cl$: Cl, 11·9%); 3 : 4-(3 : 3 : 6 : 6-tetramethyl*cyclo*hexeno)-, b. p. 185° (Found: Cl, 11·1. Calc. for $C_{21}H_{25}Cl$: Cl, 11·4%); 4-*cyclo*pentyl-, b. p. 187° (Found: Cl, 13·2. Calc. for $C_{18}H_{19}Cl$: 4-cyclo*hexyl*-, b. p. 193°, needles m. p. 62—63° from light petroleum (Found: C, 79·5; H, 7·2; Cl, 12·8. $C_{19}H_{21}Cl$ requires C, 80·1; H, 7·4; Cl, 12·5%).

Alcoholysis of the Chlorides in Anhydrous Ethyl Alcohol.—The procedure was that described by Hughes, Ingold, and Taher.[3] Experiments were carried out at 0·0°, at 20·0°, or 25·0° (±0·05°) by sampling, the samples being run into a large volume of ice-cold acetone to stop the

TABLE 3. *Ethanolysis of* 4-cyclo*pentyldiphenylmethyl chloride at* 0·0°.

t	0	50	100	135	176	230	295	348
$a - x$	11·32	9·02	7·15	6·08	5·15	4·02	2·99	2·37
10^5k	—	7·57	7·66	7·67	7·46	7·49	7·51	7·48

Mean 10^5k = 7·55; other runs gave 10^5k = 7·40 and 7·58 severally.

reaction, and titrated with sodium hydroxide (0·01N) with lacmoid as indicator. Table 3 illustrates one run. 4-*cyclo*Pentyldiphenylmethyl chloride was initially in 0·01132M-solution. Its concentration, $a - x$, at time t, in minutes, is expressed in c.c. of 0·0100N-sodium hydroxide per 10 c.c. of sample. All first-order rate constants, k, are in sec.$^{-1}$.

MANCHESTER COLLEGE OF SCIENCE AND TECHNOLOGY,
MANCHESTER, 1.

[*Received, April 18th,* 1958.]

[11] Kleene, *J. Amer. Chem. Soc.*, 1940, **62**, 3523.

XUM

888. *The Electric Dipole Moments of a Vinylenic Series.*

By M. Hely Hutchinson and L. E. Sutton.

The dipole moments of a series of compounds $Me_2N\cdot[CH{:}CH]_n\cdot CHO$, from $n = 0$ (dimethylformamide) to $n = 4$, have been measured in benzene at 25°. End-to-end charge transfers have been calculated on two very different stereochemical models, a stick-like and a snake-like one. The conclusions, which are qualitatively independent of the model used, are that this charge transfer falls off quickly as n increases. Each end-group appears to have a limited sphere of action extending over about three vinylene units.

The effect of conjugation on the dipole moments of aliphatic chain systems has received little investigation. Kushner and Smyth [1] measured dipole moments of individual dyes and compared observed moments with the number of possible ionic structures. Everard and Sutton [2] measured several series of compounds containing conjugated ring systems: they found that (with the exception of styrene derivatives) the mesomeric moments increased linearly with the length of the system.

Spectroscopists have investigated several series of vinylenic compounds: among recent publications Bohlmann and Mannhart [3] have confirmed the simple prediction by Lewis and Calvin [4] that for polyenes $\lambda_{max.} \propto \sqrt{n}$ (where n is the number of vinylene links). Whiting and Malhotra (unpublished work) subsequently observed that cyanines correspond to the other Lewis and Calvin model, with $\lambda_{max.} \propto n$, but that the vinylogues of dimethylformamide do not correspond to either model.

Simple treatment of conjugated aliphatic systems offers two alternative predictions for a rigid, " stick-like " model, wherein the end-dipoles of a series such as we have investigated would have relative orientations unaltered by the interpolation of extra vinylene links:

(*a*) Provided that the end-groups do not interact, the dipole moment of the series will be independent of n. (*b*) If, on the other hand, the end-groups do interact to give a charge transfer from end to end, the dipole moment will be a linear function of the product $(\delta e \,.\, \mathbf{r})$ where δe is the charge transferred, and $\mathbf{r}$ the distance between the end-groups. Clearly $\mathbf{r}$ is a linear function of n, and so the dipole moment will also be if δe is constant.

Measurement of the dipole moments of a series of compounds with the same end-groups should enable us to distinguish between the two possibilities (*a*) and (*b*). If the results indicate some combination of the two, then we should be able to infer to what extent " conjugation " amounts to an end-to-end charge transfer. Therefore this has been done for several vinylogues of dimethylformamide.

Experimental

Benzene of analytical grade was purified as described by Hill and Sutton.[5] The compounds $Me_2N\cdot[CH{:}CH]_n\cdot CHO$ ($n = 0$—6) were prepared by Dr. M. C. Whiting and Dr. S. S. Malhotra (to be published).

Electric dipole moments were determined by measuring dielectric constants and specific volumes at 25° by the methods described by Everard and Sutton [6] for their small-scale technique, with the heterodyne-beat capacitance meter described by Hill and Sutton.[7] The dielectric constant of benzene was assumed to be 2·2750.[8] The pyknometer was calibrated with air-free distilled water. Owing to strong absorption of light by all the solutes save dimethylformamide, refractive-index measurements were not satisfactory, and values of $_EP$ were calculated from

[1] Kushner and Smyth, *J. Amer. Chem. Soc.*, 1949, **71**, 1401.
[2] Everard and Sutton, *J.*, 1951, 2818.
[3] Bohlmann and Mannhardt, *Chem. Ber.*, 1956, **89**, 1307.
[4] Lewis and Calvin, *Chem. Revs.*, 1939, **25**, 273.
[5] Hill and Sutton, *J.*, 1949, 746.
[6] Everard and Sutton, *J.*, 1951, 16.
[7] Hill and Sutton, *J.*, 1953, 1482.
[8] Hartshorn, Parry, and Essen, *Proc. Phys. Soc.*, 1955, **68**, *B*, 422.

refractivity values. The numerical values used [9] were: H = 1·10, C = 2·42, tertiary N = 2·84, carbonyl O = 2·21, increment for (C=C) = 1·73 c.c. The derived $_{E}P$ values can be summarised by the equation $_{E}P(n) = 20{\cdot}0 + 8{\cdot}75n$ (where $_{E}P$ is expressed in c.c. and n is the number of vinylene groups). For dimethylformamide (see Table 1) the agreement between the observed value and that so calculated was fair.

The computation of moments and the notation used follow the pattern set by Everard, Hill, and Sutton,[10] so that no allowance has been made for atom polarisation other than that implicit in using $[R]_{D}$ values. As the moments are large ($\mu > 3$ D), the uncertainties in $_{E}P$ and in $_{A}P$ are unimportant.

The solubility in benzene falls off rapidly with increase in n, and no satisfactory results could be obtained for the compounds with $n = 5$ or 6. The results for $n = 0$—4 are shown in Table 1 and plotted in Fig. 1.

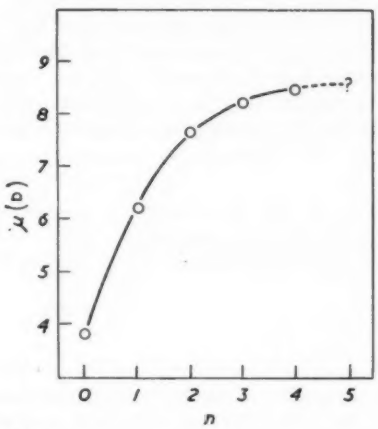


FIG. 1. *Electric dipole moment as a function of chain length.*

TABLE 1.

ε	v	$-10^5 . \Delta n$	$10^4 w$	ε	v
Dimethylformamide ($n = 0$)			($n = 3$)		
1243	2·3028	1·1445	8·5	608	2·3046	1·1448
1908	2·3164	1·1447	12·4	1559	2·3521	1·1448
4739	2·3784	1·1446	31·4	2361	2·3903	1·1447
4958	2·3836	1·1446	33·2	3316	2·4363	1·1448

$\varepsilon = 2{\cdot}2751_4 + 21{\cdot}83w$, $v = 1{\cdot}1446 + 0{\cdot}003w$, $\Delta n = -0{\cdot}067w$, $_{T}P_2 = 324{\cdot}9$ c.c., $_{E}P_2$ (calc.) = 20·0 c.c., $_{E}P_2$ (obs.) = 21·8 c.c.

$\mu = 3{\cdot}86 \pm 0{\cdot}01$ D.

$\varepsilon = 2{\cdot}2753 + 48{\cdot}68w$, $v = 1{\cdot}1448 - 0{\cdot}01w$, $_{T}P_2 = 1434{\cdot}2$ c.c., $_{E}P_2$ (calc.) = 46·2 c.c.

$\mu = 8{\cdot}24 \pm 0{\cdot}02$ D.

($n = 1$)			($n = 4$)		
685	2·3029	1·1446	433	2·2937	1·1447
2065	2·3619	1·1444	631	2·3023	1·1448
2611	2·3860	1·1445	775	2·3094	1·1449
3913	2·4416	1·1443	1182	2·3271	1·1447

$\varepsilon = 2{\cdot}2743 + 42{\cdot}71w$, $v = 1{\cdot}1446 - 0{\cdot}06w$, $_{T}P_2 = 827{\cdot}4$ c.c., $_{E}P_2$ (calc.) = 28·7 c.c.

$\mu = 6{\cdot}24 \pm 0{\cdot}02$ D.

$\varepsilon = 2{\cdot}2747 \pm 44{\cdot}20w$, $v = 1{\cdot}1448 - 0{\cdot}003w$, $_{T}P_2 = 1532{\cdot}9$ c.c., $_{E}P_2$ (calc.) = 54·9 c.c.

$\mu = 8{\cdot}50 \pm 0{\cdot}04$ D.

($n = 2$)		
855	2·3194	1·1447
1021	2·3286	1·1446
1134	2·3327	1·1446
2459	2·4005	1·1446

$= 2{\cdot}2755 + 50{\cdot}94w$, $v = 1{\cdot}1446 - 0{\cdot}002w$, $_{T}P_2 = 1240{\cdot}7$ c.c., $_{E}P_2$ (calc.) = 37·5 c.c.

$\mu = 7{\cdot}67 \pm 0{\cdot}05$ D.

[9] Landolt and Börnstein's "Tabellen," Springer Verlag, Berlin, 1923, 985.
[10] Everard, Hill, and Sutton, *Trans. Faraday Soc.*, 1950, **46**, 417.

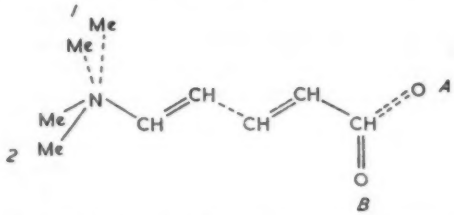
XUM

Discussion

It is immediately apparent from Fig. 1 that neither of the simple treatments, (*a*) or (*b*), is adequate to explain the observed results. We have therefore attempted to combine the two. This requires that we consider in some detail the configuration of the polyene chain.

As with any polyene system, these compounds may, in principle, have a very large number of stereoisomers. If free rotation around the "single bonds" can occur, the number of forms is infinite. If, however, we may postulate a planar skeleton we reduce isomerism to *cis–trans* and *cisoid–transoid* (*s-cis–s-trans*) types. Experimental justification for doing this comes from the examination of butadiene [11] and of acraldehyde [12] by electron diffraction and by microwave spectroscopy, respectively. The scattering pattern for butadiene can be adequately accounted for by a *transoid* structure, with no evidence for *cisoid*. Similarly, the spectrum of acraldehyde gives no definite evidence of any species being present but the *transoid*; and it is consistent with a potential function for rotation about the central C–C bond which has the *cisoid* form approximately 2·5 kcal. mole^{-1} above the *transoid*, and a *transoid* barrier height of 5 kcal. mole^{-1}.

The four different forms are 1A, 1B, 2A, and 2B.



Two principal models have been considered: (*a*) The all-*trans*, all-*transoid* "stick" model in which there are only four non-equivalent forms (see diagram) depending upon the orientation (in the plane) of the end-groups relative to the skeleton. (*b*) A "snake" model, in which no restrictions are placed upon configuration except those of planarity and the preservation of normal bond angles. This requires consideration of 2^{2n+1} possible isomers, although some of them are equivalent.

For both models, all carbon–carbon distances were assumed to be 1·40 Å; this does not lead to any major error in calculating overall lengths and vector angles in the molecules. Also all ∠CCC were assumed to be 120°. We have further simplified the treatment by assuming that for any given compound the charge transfer δe is the same for all the configuration isomers. Therefore we regard the overall dipole moment of a particular isomer ($\boldsymbol{\mu}_T$) as being made up of a charge-transfer moment ($\delta e \,.\, \mathbf{r}$) and the vector sum of the end-group moments ($\boldsymbol{\mu}_D$). If θ is defined as the angle between the vector $\boldsymbol{\mu}_D$ and the charge-transfer moment, then

$$\mu_T^2 = \mu_D^2 + (\delta e \,.\, r)^2 - 2\mu_D(\delta e \,.\, r)\cos\theta \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Since our models have more than one configuration isomer, we must take a mean of their polarisations (which are individually proportional to μ_T^2) in order to calculate an observable dipole moment. The correct mean, fortunately, is the arithmetic one, so that if each is assumed to have the same weighting factor, we have the simple relation

$$\mu^2_{obs.} \equiv \langle\mu_T^2\rangle = \langle\mu_D^2\rangle + \langle r^2\rangle(\delta e)^2 - 2\langle\mu_D r\cos\theta\rangle(\delta e) \quad . \quad . \quad . \quad (2)$$

(the assumption that δe is constant enables us to take it outside the average bracket). By rearrangement, we can obtain a simple quadratic in δe:

$$\langle r^2\rangle(\delta e)^2 - 2\langle\mu_D r\cos\theta\rangle(\delta e) - (\mu^2_{obs.} - \langle\mu_D^2\rangle) = 0 \quad . \quad . \quad (3)$$

[11] Bastiansen, personal communication.
[12] Wagner, Fine, Simmons, and Goldstein, *J. Chem. Phys.*, 1957, **26**, 634.

To obtain values of μ_D we have used aliphatic group moments taken from a critical survey:[13] C=O = 2·75 D along C=O, C–NMe_2 = 0·86 D at 109° to the N–C vector. This use of aliphatic moments attributes any mesomeric moment to the charge transfer.

From the form of the curve (Fig. 1) it is clear that it might be possible to extrapolate to obtain an approximate value for the dipole moment of the $n = 5$ compound. Linear extrapolation from the values of the $n = 3$ and $n = 4$ compounds gives the moment of $n = 5$ as 8·75 ±0·15 D; we also fitted a curve to the observed values, on the assumption that for large n the moment would reach a constant value. The curve employed was of the form $\mu = p - q(1 + rn)e^{-sn}$. This gave a value of 8·61 D for the $n = 5$ compound and a limiting value of 8·66 D. For the purposes of subsequent calculation we shall use the value of 8·6 D.

TABLE 2. *Derived charge transfer values* (in units of electron charge or units of 4·8 e.s.u.).

n	0	1	2	3	4	5
a Stick model	0·49	0·34	0·26	0·21	0·17	0·14 †
b Snake model (all forms)	0·48	0·38	0·34	0·29	0·25 *	0·22 *†
c Snake model (Class 2 forms) ...	0·49	0·41	$0·33_5$	0·27	0·23 *	0·20 *†

* By graphical extrapolation of coefficients in equation (3).
† Using the extrapolated value for $\mu_{obs.}$ = 8·6 D.

(a) *The stick model.* The results of the solution of equation (3) for the stick model are shown in Table 2, row *a*, and are plotted in Fig. 2. The single, most stable form (from dipole–dipole energies) gives results differing by less than 0·01**e** electron charge from this mean value.

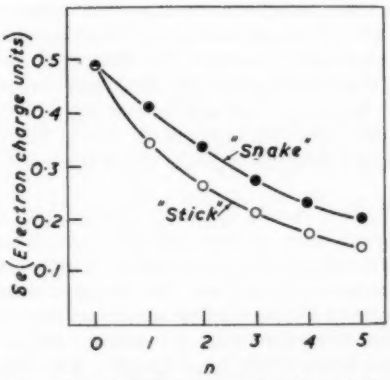


FIG. 2. *Charge transfer as a function of chain length.*

(b) *The snake model.* Although the same in principle, the averaging of the coefficients in equation (3) for the snake model is more complicated than for the stick model because of the 2^{2n+1} configurations that it may have. Certain simplifying results emerge, the principal one being that there are only six possible values of the μ_D vector. Nevertheless, the calculation becomes rather lengthy as n gets larger (there being 128 sets of terms for $n = 3$ and 512 for $n = 4$); so, for the compounds with $n > 3$ it was decided to extrapolate graphically to obtain the necessary coefficients. The $\langle r^2 \rangle$ coefficients fall on a straight line, while the curve for the $\langle \mu_D^2 \rangle$ values is monotonic in form, in the region $n = 0$ to $n = 3$: thus there is little error in a graphical extrapolation of the two sets of values $\langle r^2 \rangle$ and $\langle \mu_D^2 \rangle$. On the other hand, the cross-terms ($\langle \mu_D r \cos\theta \rangle$) lie on a curve with a maximum between $n = 1$ and $n = 2$, so that graphical extrapolation was not very accurate. Fortunately, the derived value of δe is much less sensitive to this term than to the other two.

Using, then, the calculated values for the coefficients for $n = 0$ to $n = 3$ and extrapolated values for $n = 4$ and $n = 5$ (together with the extrapolated value of the dipole

[13] Katritzky, Randall, and Sutton, *J.*, 1957, 1769.

moment for $n = 5$), we obtained the values shown in Table 2, row *b*. All the configurations were included in this average.

It seems clear, however, that all the possible configurations of these molecules will not be equally probable and that our previous assumption of equal weighting is not valid. We have, therefore, calculated the dipole–dipole interaction energies, by the standard method.[14] Comparing these with the thermal energy function kT, we found that the configurations fall into four classes: (1) those with large dipole–dipole attractive energies, but with steric hindrance; (2) those with smaller dipole–dipole attractive energies, and no steric hindrance; (3) those with small dipole–dipole repulsions, and (4) those with large dipole–dipole repulsions. Classes (1) and (4) can clearly be neglected. The configurations in each of classes (2) and (3) have energies corresponding to theoretical populations in a range of roughly 3 to 1. Since we intended to average with unit weighting or with zero weighting, we decided to consider only class (2). This contains approximately a third of the total possible configurations, for the lower members of the series.

Solving equation (3) for this type of configuration only, we obtained the values shown in Table 2, row *c*, and plotted in Fig. 2.

It seems surprising that the curves plotted in Fig. 2 should be so similar in form, but this result is very gratifying, for it means that the qualitative conclusions are insensitive to assumptions about the conformation of the chain itself and therefore are probably right. While the absolute values of the ordinates are dependent upon the detailed assumptions made, the relative values are affected very little.

In general terms we conclude that each polar end-group creates a disturbance in the conjugated chain which extends over a few links only. When two such groups, operating in the same sense, are placed so that their spheres of action overlap, they seem to create a perturbation which amounts to a considerable end-to-end charge transfer. As the groups are separated, however, this dies away. Eventually we should be left, at large values of n, with two separate dipoles, each perturbing several links of chain and causing local charge transfers, but not interacting. Thus the dipole moment should reach a constant value, and the value of δe should fall to zero. Our observations seem to be consistent with a range of action of about three vinylene groups from each of the end-groups studied.

Although these results appear to conflict with those of Everard and Sutton,[2] it should be stressed that these authors studied systems containing aromatic rings, while we have studied a series of aliphatic compounds. Further, they pointed out that their relationship between mesomeric moment and the length of system might be fortuitous, and they were unable to account for the styrene results on this picture.

It is possible to show that a benzene ring has a greater insulating effect that has a linear polyene chain of the same length. The value of the dipole moment of *p*-dimethylaminobenzaldehyde has been measured in benzene solution:[15] it is 5·6 D. The angular, *para*-end-groups have only two possible non-equivalent configurations; and solving equation (3) for either leads to a charge transfer of 0·21 electron.

Comparing this result with the " stick " values, Fig. 2, we see that a benzene ring seems to be equivalent to the $n = 3$ compound: in other words, the insulating effect of a benzene ring is roughly equal to that of a conjugated chain of three vinylene groups, though the shortest vinylene system through the benzene ring corresponds to $n = 2$. This result accentuates the difference between aliphatic and aromatic systems.

We thank Dr. M. C. Whiting for calling our attention to the problem, Dr. S. S. Malhotra for supplying the compounds, and Dr. A. D. Buckingham for helpful discussions.

THE PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, July 9th*, 1958.]

[14] See, *e.g.*, Buckingham and Pople, *Trans. Faraday Soc.*, 1955, **51**, 1173.
[15] Weizman, *ibid.*, 1940, **36**, 329.

889. *Kinetics of the Acid and Alkaline Hydrolysis of Potassium Ethoxycarbonylmethanesulphonate.*

By R. P. Bell and D. J. Rawlinson.

The rate of hydrolysis of potassium ethoxycarbonylmethanesulphonate has been measured in acid and in alkaline solution. The sulphonate group, although bearing a net negative charge, behaves as a weakly electron-attracting group. Supporting evidence for this statement is quoted, and an explanation given in terms of the structure of the sulphonate group. In concentrated acid solution the velocity of hydrolysis follows the acid concentration more closely than the acidity function, in agreement with previous findings for ester hydrolysis.

Previous papers [1,2] on the hydrolysis of ethoxycarbonylmethyltriethylammonium iodide dealt with the effect of a positively charged substituent upon the kinetics of ester hydrolysis, and the present work was planned to give corresponding information about the effect of a negative group. For alkaline hydrolysis this information is available from the rates of successive stages of hydrolysis of dicarboxylic esters, but this approach is not possible for acid hydrolysis since the carboxylate group does not retain its negative charge in acid solution. This difficulty does not arise with sulphonates, which are derived from strong acids: however, it will be seen that the sulphonate group does not behave as a simple negative pole.

Experimental

Potassium ethoxycarbonylmethanesulphonate (subsequently referred to as "ester") has been prepared by Andreasch [3] from ethyl monochloroacetate and potassium sulphite and by Vieillefosse and Vieillefosse [4] by esterifying sulphoacetic acid and isolating the barium salt. We used a modification of the former method. Equivalent quantities of the two reactants were dissolved in the minimum quantity of water containing 20% of ethanol and refluxed for 30 mins. After evaporation to dryness the solid mass was extracted with boiling 90% ethanol from which the ester crystallised on cooling. After further recrystallisation from 90% ethanol or from ethanol–glycol (19 : 1) the ester (yield 25%) had m. p. 212°. Andreasch [3] gives m. p. 183°. Quantitative hydrolysis by acid or alkali, as described in the kinetic experiments, indicated a purity of 100 ± 1%. Other reagents used were "AnalaR."

In most kinetic measurements the reaction was followed by titration, but this was not practicable for acid concentrations greater than about 2M, for which dilatometry with two conventional dilatometers having volumes of 25 and 50 c.c. and capillaries of 0·1 mm.^{2} cross-section was used. The ester concentrations were in the range 0·1—0·5M so as to give a movement of 8—15 cm. in the capillary for complete reaction. First-order kinetics were observed, and velocity constants were obtained graphically by use of an observed end-point for fast reactions and Guggenheim's method [5] for slow ones. There was good agreement between the dilatometric and titration methods in the concentration range where they overlap. In the titration method for acid hydrolysis the product $SO_3^-{\cdot}CH_2{\cdot}CO_2H$ (pK 4·1) [6] was titrated (together with the catalyst acid) with standard alkali, Phenol Red being used as indicator. The first-order velocity constants were obtained graphically by use of the calculated titre for complete hydrolysis. For alkaline hydrolysis approximately equal concentrations (0·005M) of ester and sodium hydroxide were used. Samples were added at intervals to an excess of 0·01N-hydrochloric acid, and the excess of acid titrated with 0·006N-sodium hydroxide (Phenol Red). The second-order velocity constants were obtained graphically from a plot of log $\{(a - x)/(b - x)\}$ against time. In all titrations the solution was kept free from carbon dioxide by a stream of nitrogen.

[1] Bell and Waind, *J.*, 1950, 1979.
[2] Bell and Lindars, *J.*, 1954, 4601.
[3] Andreasch, *Monatsh.*, 1926, **46**, 639.
[4] Vieillefosse and Vieillefosse, *Bull. Soc. chim. France*, 1947, 256.
[5] Guggenheim, *Phil. Mag.*, 1926, **2**, 538.
[6] Backer, *Proc. Acad. Sci. Amsterdam*, 1922, **25**, 359; 1923, **26**, 83.

XUM

The results of the kinetic measurements are given in Tables 1—3, k_1 being the first-order velocity constant (sec.$^{-1}$) and k_2 the second-order one (l. mole^{-1} sec.$^{-1}$). Some solutions contained high concentrations both of acid and of ester, and in these there is a considerable difference between the molality m and the molarity c of the catalyst. Both are given, the measured densities of the solutions being used to inter-relate them.

TABLE 1. *Acid hydrolysis at 25°, by dilatometry.*

	c	m	10^7k_1
HCl	1·94	2·16	148
	1·95	2·16	144
	3·08	3·36	276
	4·45	5·22	430
	5·94	7·22	677

	c	m	10^7k_1
HCl	7·18	8·69	861
	7·54	9·29	1180
	7·78	9·52	1020
	8·87	12·21	1270
	10·39	15·44	1690

	c	m	10^7k_1
H_2SO_4	1·54	1·74	142
	3·44	4·12	390
	4·72	5·99	589
	5·71	7·79	793

TABLE 2. *Acid hydrolysis, by titration at 25° (except those marked,* which are at 45°).*

HCl			
10^3c	10^3m	10^2[KCl]	10^7k_1
2·59*	2·59*	—	16·6*
5·19*	5·19*	—	31·0*
1·24	1·24	—	1·34
1·24	1·24	1·34	1·22
1·24	1·24	2·68	1·18
1·24	1·24	4·53	1·14

HCl		
10^3c	10^3m	10^7k_1
4·7	5·1	3·88
9·4	10·0	7·94
22·8	23·8	17·6
57·9	60·4	48·7
99·4	105	70·7
191	216	121

H_2SO_4		
10^3c	10^3m	10^7k_1
11·0	11·6	11·3
22·0	23·2	19·1
44·0	45·9	48·5
211	248	224

TABLE 3. *Alkaline hydrolysis, by titration.*

At 0°		
10^3[KCl]	10^3I	10^3k_2
—	9·41	35·9
21·1	30·6	39·2
52·8	62·3	41·2
106	115	48·3
106	115	51·1

At 25°		
10^3[KCl]	10^3I	10^3k_2
—	9·6	146
21·1	30·8	167
52·8	62·5	193
106	115	215

At 35°		
10^3[KCl]	10^3I	10^3k_2
—	9·6	255
52·8	62·5	331
106	115	372

At 45°		
10^3[KCl]	10^3I	10^3k_2
—	9·4	438
21·1	30·6	504
52·8	62·3	557
62·3	71·7	586
84·5	93·9	658
106	115	634

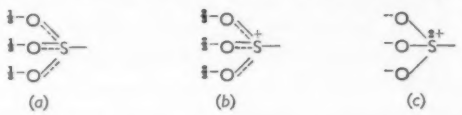
DISCUSSION

The results show the large salt effects to be expected for reactions between two ions. The data are most extensive for alkaline hydrolysis, and the Figure shows plots of log k_2 against $I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}})$ at four temperatures. The lines are drawn with the theoretical slope of unity (the small temperature-dependence of the dielectric constant being neglected): this is in good agreement with experiment, and the velocity constants can be readily extrapolated to zero ionic strength. The extrapolated values at 0°, 25°, 35°, and 45° are k_2° = 0·0275, 0·120, 0·209, and 0·363 l. mole^{-1} sec.$^{-1}$, which are well represented by the Arrhenius equation $k_2^\circ = 2{\cdot}30 \times 10^6 \exp(-9920/\boldsymbol{RT})$. The results for hydrolysis by dilute acid show a similar salt effect in the opposite direction, and the results in 0·0124M-hydrochloric acid can be extrapolated by using the theoretical slope to give $k^\circ/c = 1{\cdot}44 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$ at zero ionic strength at 25°.

Although the salt effects show the behaviour expected for an ester containing a negatively charged substituent this is not so for the actual values of the velocity constants. Previous comparisons [1,2] of the ester $^+NEt_3{\cdot}CH_2{\cdot}CO_2Et$ with ethyl acetate showed that the presence of the group $-^+NEt_3$ increases the rate of alkaline hydrolysis 200-fold and decreases that of acid hydrolysis 2000-fold, and the group $-SO_3^-$ might be expected to show effects of similar magnitude in the opposite direction, especially since $CO_2Et{\cdot}CH_2{\cdot}CO_2^-$ is hydrolysed by alkali 65 times more slowly than $CH_2(CO_2Et)_2$.[7] Actually, however, our results show that at 25° the species $SO_3^-{\cdot}CH_2{\cdot}CO_2Et$ is hydrolysed by alkali about 1·2 times as fast as ethyl acetate, and by acid about eight times more slowly. The key to this behaviour is to

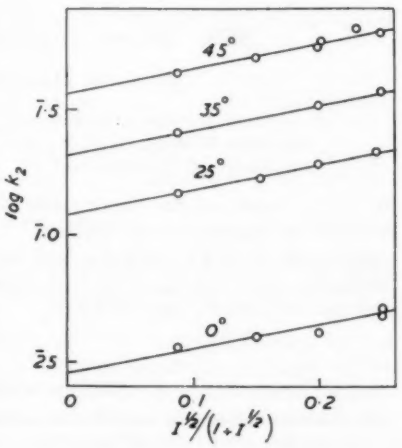
[7] International Critical Tables, Vol. VII, p. 135.

be found in the electronic structure of the sulphonate group. Various views have been expressed about the nature of sulphur–oxygen links, corresponding to the annexed formulations of the group $-SO_3^-$. It has been maintained [8] on the basis of observed bond-lengths that compounds of this class contain essentially double bonds between sulphur and oxygen, corresponding to structure (*a*), but this conclusion has been doubted [9] and the question appears to be open. In the present context structure (*a*) should certainly act as a strongly electron-repelling group, but structure (*c*) [and to a less extent (*b*)] could well act as an



(*a*) (*b*) (*c*)

electron-attracting group at short distances, since the positive charge on sulphur will then be more important than the more distant negative charge on oxygen. The kinetic results obtained here can therefore be accounted for if it is supposed that the bonds in the sulphonate group are essentially single, with a large positive charge on the sulphur atom. This explanation is not inconsistent with the observed salt effects in dilute solution, which depend upon long-range interionic forces and this involves only the net charge on the molecule.



Other evidence exists for the electron-attracting power of the sulphonate group at short distances. The pK of $SO_3^-\cdot CH_2\cdot CO_2H$ is 4·05, compared with 4·75 for acetic acid and 5·36 for $CO_2^-\cdot CH_2\cdot CO_2H$: similarly p$K$ for $CH_3\cdot{}^+NH_3$ is 10·63 but pK for $SO_3^-\cdot CH_2\cdot{}^+NH_3$ is 5·75,[10] the greater effect in the second case being due to the smaller distance between the sulphonate group and the dissociating proton. It is also relevant that the sulphonate group is weakly *meta*-directing in benzene substitution,[11] in contrast to the *ortho–para*-directing effect of other negatively charged groups.

It is of interest to consider how the effect of the sulphonate group should vary with its distance from the part of the molecule being considered, its structure being assumed to resemble (*c*). It follows from simple electrostatics that, as the distance increases, its electron-attracting power should decrease and change to repulsion at a distance of a few Ångström units. The electron-repulsion should then at first increase with increasing distance, but should soon pass through a maximum and finally decrease to zero. Data are not available for the series $SO_3^-\cdot[CH_2]_n\cdot CO_2H$ or the corresponding esters, but the acid strengths of the series [10] $SO_3^-\cdot[CH_2]_n\cdot{}^+NH_3$, with p$K$ in parentheses following, are n: 1 (5·75), 2 (9·20), 3 (10·05), 4 (10·65), 5 (10·95), 10 (11·35). Since pK in the series $CH_3\cdot[CH_2]_n\cdot{}^+NH_3$ is almost constant at 10·62 ± 0·03, these figures show the expected changes of sign in effect of the sulphonate group at about $n = 4$. The effective distance between the groups probably does not continue to increase for large values of n, since the chain is flexible and the oppositely charged ends will tend to approach one another. An analogous increase in electron-repelling power with distance is observed

[8] Hunter, Phillips, and Sutton, *J.*, 1945, 146.
[9] Wells, *J.*, 1949, 55.
[10] Rumpf, *Bull. Soc. chim. France*, 1938, **5**, 87.
[11] Ingold, "Structure and Mechanism in Organic Chemistry," Methuen, London, 1953, p. 235.

in the compounds $SeO_2^-\cdot CH_2\cdot CO_2H$ (pK 5·43) and $SeO_2^-\cdot[CH_2]_2\cdot CO_2H$ (pK 5·99)[12] and can be explained similarly.

The kinetic measurements in concentrated acid solution (cf. Table 1) show that the reaction velocity increases somewhat more rapidly than the acid concentration (whether expressed as molality or molarity), but a great deal more slowly than the acidity function H_0. Since the ester has a negative charge the appropriate acidity function is H_- rather than H_0, but the meagre evidence available suggests that these two functions do not differ greatly.[13] The lack of parallelism between velocity and acidity function indicates that the transition state is not formed by the simple addition of a proton to the ester but probably also contains a water molecule: the same conclusion has been reached for the acid hydrolysis of uncharged esters.[14]

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, July 28th*, 1958.]

[12] Backer and van Dam, *Rec. Trav. chim.*, 1930, **49**, 482.
[13] Paul and Long, *Chem. Rev.*, 1957, **57**, 1.
[14] Chmiel and Long, *J. Amer. Chem. Soc.*, 1956, **78**, 3326; Bell, Dowding, and Noble, *J.*, 1955, 3106.

---

890. *Higher Complex Fluorides of Molybdenum.*

By G. B. HARGREAVES and R. D. PEACOCK.

From the interaction of molybdenum hexafluorides with alkali fluoride the salts K_2MoF_8, K_3MoF_8, $RbMoF_7$, $RbMoOF_5$, and $CsMoOF_5$ have been obtained and characterised.

DURING a study of the fluorination of tungsten carbonyl a number of higher complex fluorides of tungsten were isolated.[1] We now show that molybdenum forms similar compounds, K_2MoF_8, K_3MoF_8, and $RbMoF_7$. In addition, two complex oxyfluorides, $RbMoOF_5$ and $CsMoF_5$, have been characterised and we submit X-ray evidence for the existence of $CsMoF_7$ and $NaMoOF_5$.

TABLE 1.

Reagents	Solid products
1. Reactions starting from molybdenum carbonyl and excess of iodine pentafluoride	
$Mo(CO)_6 + IF_5$	MoF_6, MoF_4?
$MI + Mo(CO)_6 + IF_5$	$MMoF_6$ *
$2KI + Mo(CO)_6 + IF_5$	K_2MoF_8
$2MI + Mo(CO)_6 + IF_5$	$KMoF_6 + MF$ †
$CsF + Mo(CO)_6 + IF_5$	$CsMoF_6$
2. Reactions of molybdenum hexafluoride and alkali fluoride	
(*a*) In iodine pentafluoride	
$NaF + MoF_6 + IF_5$	NaF
$KF + MoF_6 + IF_5$	K_2MoF_8
$RbF + MoF_6 + IF_5$	$RbMoF_7$
$CsF + MoF_6 + IF_5$	$CsMoF_7$
$RbF + MoF_6 + IF_5$ §	$RbMoOF_5$
$CsF + MoF_6 + IF_5$ §	$CsMoOF_5$
(*b*) In liquid sulphur dioxide	
$KF + MoF_6 + SO_2$	K_2MoF_8
$RbF + MoF_6 + SO_2$	$RbMoOF_5$
$CsF + MoF_6 + SO_2$	$CsMoOF_5$
(*c*) In arsenic trifluoride	
$CsF + MoF_6 + AsF_3$	$CsMoOF_5$
3. Reactions of rhenium hexafluoride and alkali iodide	
$MI + ReF_6 + IF_5$	$MReF_6$ ‡
4. Reaction of rhenium hexafluoride and potassium fluoride	
(*a*) In iodine pentafluoride	
$KF + ReF_6 + IF_5$	K_2ReF_8
(*b*) In liquid sulphur dioxide	
$KF + ReF_6 + SO_2$	K_2ReF_8

* M = Na, K, Rb, Cs. † M = Na, Rb. ‡ M = K, Rb, Cs. § Slightly moist.

As in the work with tungsten,[1] the chief experimental difficulty was to distinguish true compounds from mixtures. Preparative methods are summarised in Table 1, which

[1] Hargreaves and Peacock, *J.*, 1958, 2170.

shows that the products obtained are not always analogous to those from parallel reactions of tungsten. In iodine pentafluoride solution sexivalent molybdenum is more readily reduced to the quinquevalent state than sexivalent tungsten, so that interaction between molybdenum or rhenium hexafluoride and alkali iodides gives fluoromolybdates(v) and fluororhenates(v) (cf. ref. 2). At first we attributed this reduction to dissolved iodine from the alkali iodide, but later work has suggested that the active agent is the tetrafluoroiodate(III) ion, IF_4^-.

The three salts K_2MoF_8, $RbMoF_7$, and $CsMoF_7$ have similar properties to their tungsten analogues. They are stable to 150° in a vacuum and remain unchanged in a dry atmosphere. When exposed to moist air, however, they soon attack glass containers and turn blue; solid molybdenum hexafluoride behaves in a similar way. They are slightly paramagnetic ($\mu_{eff.}$ 0·2 B.M.) at room temperature, like the corresponding tungsten salts. Debye *X*-ray photographs show that the higher complex fluorides K_2MoF_8, $RbMoF_7$, and $CsMoF_7$ are structurally related to the higher fluorotungstates (Table 2); the densities indicate that the unit-cells of K_2MoF_8 and $RbMoF_7$ each contain 48 fluorine atoms.

The oxypentafluorides $MMoOF_5$ (M = Na, Rb, Cs) are isostructural with the hexafluoromolybdates $MMoF_6$, and in fact the unit-cell sizes of corresponding compounds are practically the same. As with tungsten, there is no potassium salt; perhaps the tetragonal

TABLE 2.

	Unit-cell size * (Å)	Density (obs.)	Density (calc.)	Fluorine atoms per unit cell
K_2MoF_8	10·01 C	3·19	3·23	48
$RbMoF_7$	10·25 C	3·46	3·33	48
$CsMoF_7$	5·36 C	—	—	—
K_3MoF_8	14·1 C	—	—	—

	Unit-cell size (Å)
$NaMoOF_5$	8·19 C
$RbMoOF_5$	5·12 (96·5°) R
$CsMoOF_5$ ...	5·29 (96·0°) R

* C = cubic; R = rhombohedral.

$KMoF_6$ structure which, like the $KNbF_6$ structure recently described [3] must contain two shorter Mo–F bonds in each MoF_6^- octahedron, is not sufficiently flexible to allow the easy replacement of fluorine by oxygen.

The quinquevalent complex K_3MoF_8 has a cubic unit-cell. Only potassium salts of the series $M_3Mo^VF_8$ and $M_3W^VF_8$ have been made; this is perhaps a measure of the stability of the several $MMoF_6$ and MWF_6 lattice structures. Tripotassium octafluoromolybdate is hydrolysed immediately by water; the first effect is the formation of a deep reddish brown solution quite different in appearance from the blue solution given by potassium hexafluoromolybdate(v) $KMoF_6$, but similar to that given by the mixture " Rb_3MoF_8," so that the only reliable way of distinguishing $MMoF_6 + 2MF$ from M_3MoF_8 is by Debye *X*-ray photographs.

In view of the existence of complexes between the alkali fluorides and the hexafluorides of molybdenum and tungsten, it will be interesting to know whether ReF_6, OsF_6, OsF_8, IrF_6, the recently discovered PtF_6, UF_6, and the hexafluorides of the actinides behave similarly. We have good reason to believe from preliminary experiments that ReF_6 does form such compounds; with the platinum-metal fluorides it may be difficult to find a suitable solvent to promote combination. So far as other hexafluorides are concerned, fluorotellurates(VI) such as Cs_2TeF_8 have recently been isolated; [4,5] SF_6 and SeF_6 are probably too inert to combine with alkali fluorides.

EXPERIMENTAL

1. *Reactions starting from Molybdenum Carbonyl and Iodine Pentafluoride.*—(a) $Mo(CO)_6$ *alone.* In the cold with excess of IF_5, molybdenum hexafluoride was formed which was

[2] Hargreaves and Peacock, *J.*, 1957, 4212.
[3] Bode and Döhren, *Acta Cryst.*, 1958, **11**, 80.
[4] Muetterties, *J. Amer. Chem. Soc.*, 1957, **71**, 1004.
[5] Muetterties and Phillips, *J. Amer. Chem. Soc.*, 1957, **71**, 2975.

identified by its physical properties. With excess of $Mo(CO)_6$ impure molybdenum tetrafluoride remained as a reddish brown solid (Found: Mo, 59·6; F, 41·2%. Calc. for an equivalent mixture of MoF_3 and MoF_4: Mo, 59·1; F, 40·9%), magnetic moment $\mu_{eff.} = 2·45$ B.M. at 25° ($\mu_{eff.}$ $MoF_4 = 2·3$ B.M.).

(b) *Mixture* $Mo(CO)_6 : MI = 1 : 1$. When warmed with excess of iodine pentafluoride this produced white quinquevalent hexafluoromolybdates, which were readily freed from excess of iodine at 150° (Found: Mo, 40·7; F, 48·5. Calc. for $NaMoF_6$: Mo, 41·2; F, 48·4. Found: Mo, 38·7; F, 45·4. Calc. for $KMoF_6$: Mo, 38·5; F, 45·8. Found: Mo, 32·3; F, 37·3. Calc. for $RbMoF_6$: Mo, 32·5; F, 38·6. Found: Mo, 28·0; F, 34·0. Calc. for $CsMoF_6$: Mo, 28·0; F, 33·3%).

(c) *Mixture* $Mo(CO)_6 : KI = 1 : 2$. Treatment of this mixture with iodine pentafluoride yielded a white solid which could be freed from iodine and iodine pentafluoride by heating it in a vacuum at 150° for 30 min. This was *tripotassium octafluoromolybdate*(v) (Found: Mo, 26·0; F, 40·8. K_3MoF_8 requires Mo, 26·3; F, 41·6%) which is stable, like K_3WF_8, to dry air, but decomposed by moist air. Its aqueous solution is reddish brown. Debye *X*-ray powder photographs show a cubic unit-cell with $a_0 = 14·07$ Å, and the magnetic moment is $\mu_{eff.} = 1·23$ B.M. at room temperature.

(d) *Mixture* $Mo(CO)_6 : NaI = 1 : 2$. Quinquevalent molybdenum was produced in the reaction of this mixture with iodine pentafluoride, but although the product analysed to Na_2MoF_7 (Found: Mo, 34·9; F, 47·3. Calc. for Na_2MoF_7: Mo,34·9; F, 48·4%), Debye *X*-ray photographs showed the presence of $NaMoF_6$ only, so that the product was a mixture.

(e) *Mixture* $Mo(CO)_6 : RbI = 1 : 2$. The material produced when these reagents interacted with iodine pentafluoride was again a mixture, but of the composition Rb_3MoF_8 (Found: Mo, 19·8; F, 32·7. Calc. for Rb_3MoF_8: Mo, 19·1; F, 30·1%). Like the compound K_3MoF_8 this gives a reddish brown aqueous solution, but Debye *X*-ray photographs showed only the presence of $RbMoF_6$.

(f) *Mixture* $Mo(CO)_6 : CsF = 1 : 1$. This mixture was used in an attempt to obtain $CsMoF_7$ after it had been realised that sexivalent molybdenum is not formed in iodine pentafluoride solution in the presence of iodide. However, the behaviour of the product towards water showed it to contain Mo^{5+}, and Debye *X*-ray photographs confirmed the presence of $CsMoF_6$.

(2). *Reactions of Molybdenum Hexafluoride and Alkali Fluoride.*—(a) *In the presence of iodine pentafluoride.* A mixture of iodine pentafluoride and excess of molybdenum hexafluoride was condensed on the finely ground dried alkali fluoride. After sufficient time (about 30 min.) had been allowed to complete the reaction, the excess of volatile fluorides was removed at 150° in a vacuum. In each case white residues remained. Sodium fluoride was recovered unchanged but, with potassium fluoride, *dipotassium octafluoromolybdate*(vi) was formed (Found: Mo, 29·7; F, 44·0. K_2MoF_8 requires Mo, 29·4; F, 46·6%). Rubidium fluoride gave *rubidium heptafluoromolybdate*(vi) (Found: Mo, 29·0; F, 40·3. $RbMoF_7$ requires Mo, 30·5; F, 42·3%). With cæsium fluoride the take-up of molybdenum hexafluoride was incomplete (Found: Mo, 21·0%. Calc. for $CsMoF_7$: Mo, 26·5%). Debye *X*-ray photographs confirmed that the principal phase was $CsMoF_7$. Slightly moist rubidium and cæsium fluorides yielded the *oxypentafluoromolybdates*(vi) (Found: Mo, 32·3; F, 34·1. $RbMoOF_5$ requires Mo, 32·8; F, 32·5. Found: Mo, 29·1; F, 28·2. $CsMoOF_5$ requires Mo, 28·3; F, 28·0%). These conclusions were supported by Debye *X*-ray photographs. Slightly moist sodium fluoride yielded an impure residue which contained some Mo^{6+}. Debye *X*-ray photographs showed the presence of $NaMoOF_5$ and NaF.

(b) *In the presence of liquid sulphur dioxide.* The experimental technique was identical with that used in the preparation of the hexafluororhenates(v). With sodium fluoride no combination took place, but with potassium fluoride Debye *X*-ray photographs confirmed the formation of K_2MoF_8. Rubidium and cæsium fluorides gave complex oxyfluorides (Found: Mo, 32·5; F, 34·0. Calc. for $RbMoOF_5$: Mo, 32·5; F, 32·5. Found: Mo, 29·1; F, 32·4. Calc. for $CsMoOF_5$: Mo, 28·3; F, 28·0%).

(c) *In the presence of arsenic trifluoride.* Arsenic trifluoride was dried over anhydrous sodium fluoride before use. Cæsium fluoride again gave only the oxypentafluoromolybdate, a conclusion supported by Debye *X*-ray photographs (Found: Mo, 30·6; F, 28·3%. Long exposure of molybdenum hexafluoride to either sulphur dioxide or arsenic trifluoride resulted in the formation of some Mo^{5+} as shown by the appearance of blue colours on the surface of the Pyrex apparatus.

XUM

3. *Reaction of Rhenium Hexafluoride and Alkali Iodide in Iodine Pentafluoride.*—Rubidium iodide gave rubidium hexafluororhenate(v) as a white powder (Found: Re, 49·9; F, 28·3. Calc. for $RbReF_6$: Re, 48·3; F, 29·5%). This conclusion was confirmed by Debye *X*-ray photographs, as was the formation of the corresponding salts from potassium and cæsium iodide.

4. *Reaction of Rhenium Hexafluoride and Potassium Fluoride.*—In the absence of a solvent, no combination takes place, but in the presence of iodine pentafluoride, impure dipotassium octafluororhenate(VI) is formed (Found: K equiv., 270. Calc. for K_2ReF_8: 416·5). Debye *X*-ray photographs showed the presence of potassium fluoride in the product. Combination was also incomplete in the presence of liquid sulphur dioxide as solvent. Potassium octafluororhenate(VI) is a green solid which dissolves in water to give a green solution which hydrolyses on long standing or on boiling.

Analysis.—Molybdenum. The complexes were dissolved in water (quinquevalent molybdenum if present was oxidised with hydrogen peroxide) and fluorine was removed by evaporating the solutions to dryness with a few ml. of perchloric acid. Molybdenum trioxide was redissolved in dilute alkali and the molybdenum estimated either as the oxine complex or as silver molybdate.

Rhenium. The complexes were broken down by mixing them with a large excess of moist fusion mixture and heating gradually in air to incipient redness. Rhenium was determined as nitron per-rhenate.

Fluorine. The compound was heated with dilute sulphuric acid and fluorine determined in the fluorosilicic acid distillate by precipitation as lead chlorofluoride and estimation of the chloride equivalent by the Volhard method.

X-*Ray Photography and Densities.*—The methods used were similar to those described for tungsten. The results appear in Table 2.

We thank Mining and Chemical Products Ltd. for a gift of cæsium salts, Imperial Chemical Industries Limited, General Chemicals Division, for the use of a fluorine cell, the University of London for silica apparatus, and the Department of Scientific and Industrial Research for a maintenance grant (to G. B. H.).

IMPERIAL COLLEGE, LONDON, S.W.7. [*Received, August 5th,* 1958.]

---

891. *The Constitution and Synthesis of Anisoxide.*

By D. H. R. BARTON, A. BHATI, P. DE MAYO, and G. A. MORRISON.

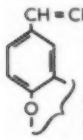
The structure (II) has, by degradation, been established for anisoxide. This conclusion has been confirmed by the synthesis of anisoxide and some of its degradation products.

THE substance, anisoxide, was first isolated by Jackson and Short,[1] from star anise oil (*Illicium verum*); they established for it the empirical formula $C_{14}H_{18}O$ and adduced evidence for its constitution which may be summarised as follows. The oxygen function was shown to be present in a cyclic ether, probably not 1 : 2 or 1 : 3, since it did not react with phenylmagnesium bromide at 100°. Of the remaining four double-bond equivalents one was shown to be present in an ethylidene grouping since ozonolysis produced acetaldehyde. Reduction with sodium and ethanol afforded dihydroanisoxide with loss of the ethylidene group. Energetic catalytic hydrogenation gave a saturated perhydroanisoxide, $C_{14}H_{26}O$, indicating that anisoxide was bicyclic. One further *C*-methyl group, probably attached to the carbon atom bearing the ethereal oxygen, was shown to be present by Kuhn–Roth determination and by fission of the oxide followed by oxidation to a ketone giving a positive iodoform test. Important results were also obtained by oxidation of anisoxide itself with potassium permanganate. The first product was an " acid A," $C_{12}H_{14}O_3$, produced by oxidation of the ethylidene group. Further oxidation of " acid A " gave " acid B," to which the formula $C_{11}H_{12}O_3$ was attributed and, finally, an " acid C,"

[1] Jackson and Short, *J.*, 1937, 513.

$C_{11}H_{10}O_4$. Through the kindness of the late Dr. W. F. Short, who provided us with his remaining material, we have been able to re-investigate the constitution of this interesting substance.

The ultraviolet spectrum of anisoxide [$\lambda_{max.}$ 265 (ε 18,740) and 302 mμ (ε 3700)] immediately suggested a close relationship with anethole [2] which was confirmed by the resemblance of the spectrum of dihydroanisoxide [1] [$\lambda_{max.}$ 231 (ε 6700) and 286 mμ (ε 3200)] to that of dihydroanethole. Further, these conclusions were confirmed by the infrared spectrum (see p. 4395) which also (bands at 741, 784, 826, 852, and 1000 cm.$^{-1}$) suggested a 1 : 3 : 4-trisubstituted benzene ring. This, together with Jackson and Short's findings,[1] suggested strongly the partial formula (I) for anisoxide. However none of the several possibilities implied by formula (I) was fully in accord with the degradative evidence previously obtained. In particular the loss of one carbon atom in " acid B " was not readily rationalised. For this reason the oxidative degradation of anisoxide was re-investigated.



(I)

The first product, obtained by oxidation with potassium permanganate in pyridine solution, was found to be a neutral glycol $C_{14}H_{20}O_3$, evidently formed by addition to the double bond. Further oxidation then gave " acid A " having $\lambda_{max.}$ 264 mμ (ε 12,000) and thus resembling anisic acid, corresponding, as suggested by Jackson and Short,[1] to the loss of the ethylidene chain. Further oxidation of " acid A" with alkaline potassium permanganate gave a hydroxy-acid, $C_{12}H_{14}O_4$, and *not* the " acid B " described by the earlier workers. This discrepancy was resolved when it was found that the hydroxy-acid was unstable to warm acetic acid in which it was dehydrated to " acid B." Since the " acid B " was originally crystallised from acetic acid it must be presumed that dehydration took place during purification. We now find that " acid B " has the empirical formula $C_{12}H_{12}O_3$ and, since it gives formaldehyde on ozonolysis together with " acid C," which has the spectral properties of an acetophenone, it must contain a methylidene group. Finally, " acid C," obtained in this manner and by potassium permanganate oxidation of " acid B," was reconverted, by reaction with methylmagnesium iodide, into the hydroxy-acid, now to be formulated as (V). On this basis anisoxide may be represented as (II), the glycol as (III), and acids A, B, and C as (IV), (IX), and (VIII) respectively. This relation was confirmed by hydrogenation of acid (IX) to give back " acid A" (IV). " Acid A" agrees in m. p. with a compound of the same structure synthesised by Lauer and Moe.[3] The structure (II) accounts in a simple manner for all the available evidence. In particular, the adduct with maleic anhydride [1] is probably of the type described by Hudson and Robinson [4] for *p*-methoxylated β-alkylstyrenes.

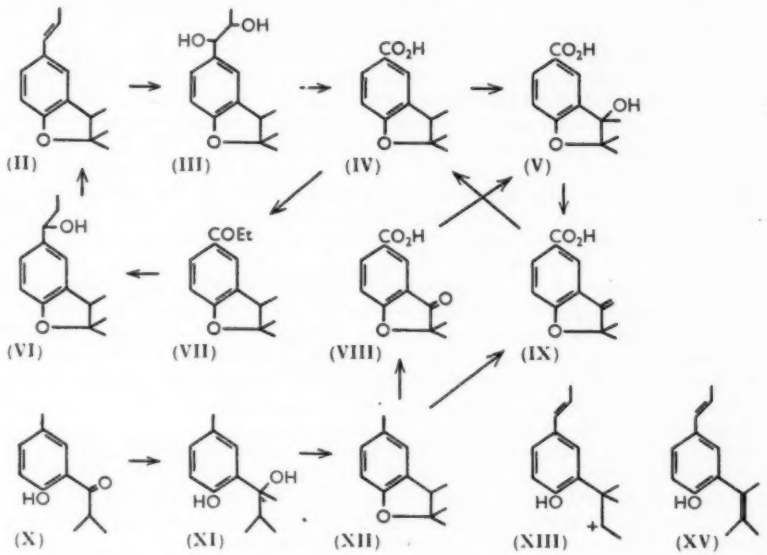
In view of the unusual arrangement of the isoprenoid side chain, so far as we are aware unique in Nature, it was considered necessary to confirm the structure (II) by synthesis. 2-Hydroxy-5-methyl*iso*butyrophenone (X) was converted by reaction with methylmagnesium iodide into the alcohol (XI). This was dehydrated and cyclised by perchloric acid in acetic acid directly to the dihydrobenzofuran (XII). Oxidation with chromic acid then gave " acid C " (VIII). Oxidation with aqueous potassium permanganate followed by dehydration gave " acid B " (IX), the conversion of which into " acid A " (IV) has already been described.

" Acid A " was converted into the corresponding ethyl ketone (VII) by reaction of the acid chloride with diazoethane followed by reduction with hydriodic acid and with zinc in acetic acid. Reduction to the alcohol (VI) was easily effected with potassium borohydride, but dehydration of the latter to anisoxide presented initially some difficulty because of the ready polymerisation of anisoxide itself. Distillation from iodine gave anisoxide (II) in small yield, but the method of choice proved to be hot aqueous-ethanolic

[2] Kharasch and Kleiman, *J. Amer. Chem. Soc.*, 1943, **65**, 11.
[3] Lauer and Moe, *ibid.*, 1943, **65**, 289.
[4] Hudson and Robinson, *J.*, 1941, 715.

hydrochloric acid, which gave a yield of about 20% of anisoxide, identical with the authentic material.

The unusual method of attachment of the isoprenoid residue of anisoxide has already



been referred to above. It appears that isoprenoid residues are in general attached to aromatic rings at position 1 or 3 (of $\overset{1}{C}-\overset{2}{C}-\overset{3}{C}\!\!<$), corresponding to the electrophilic carbons of a postulated carbonium ion (XIV). The attachment at position 2 observed in anisoxide suggests either a new type of biogenetic mechanism or, more probably, a rearrangement of (say) the carbonium ion (XIII) at some stage in the biogenesis. Such a rearrangement is encountered, for instance, in the chemistry of dunnione.[5]

$\overset{+}{H_2C-CH}-CMe_2$
(XIV)

Anisoxide is also peculiar in being optically inactive although containing an asymmetric centre. It is conceivable that the relatively drastic method of working up[1] the oil has caused racemisation. However, it is also possible that star anise oil really contains a readily cyclised unsaturated precursor of anisoxide, for example (XV), which lacks asymmetry.

Experimental

Ultraviolet absorption spectra were determined for ethanol solutions with the Unicam S.P. 500 Spectrophotometer. Infrared spectra are for liquid films unless otherwise stated. Light petroleum refers to the fraction of b. p. 40—60°. Microanalyses were carried out by Mr. J. M. L. Cameron (Glasgow) and Miss J. Cuckney (Imperial College) and their associates.

Anisoxide (II).—The material as received was partially resinified. It was purified by fractionation and the fraction of b. p. 142—143°/14 mm. was collected and crystallised from ice-cold methanol, to give pure anisoxide, m. p. (Kofler) 34—37° (Found: C, 82·95; H, 9·5. Calc. for $C_{14}H_{18}O$: C, 83·1; H, 8·95%), $\nu_{max.}$ 3005, 1610, 1488 (benzenoid), 963 (*trans*-disubstituted ethylenic linkage), 1254, 1138, and 1006 cm.$^{-1}$ (aryl ether).

Oxidation of Anisoxide (II).—To an ice-cold solution of anisoxide (2·02 g.) in pyridine (60 ml.)

[5] Price and Robinson, *J.*, 1939, 1522; 1940, 1493.

was added with stirring during 1 hr. 2% aqueous potassium permanganate (128 ml.). After being stirred for a further three hours and kept overnight the manganese dioxide was removed by filtration and the neutral material isolated with ether. After evaporation the residual gum (1·3 g.) was dissolved in ether–light petroleum (5 : 2) and filtered through a short column of silica gel. Crystallisation of the product from light petroleum and from benzene–light petroleum gave the glycol, 5-(1 : 2-*dihydroxypropyl*)-2 : 2 : 3-*trimethylbenzofuran* (III), m. p. 78—80°, $\lambda_{max.}$ 233 (ε 8770) and 285 mμ (ε 3200) (Found: C, 71·25; H, 8·3. $C_{14}H_{20}O_3$ requires C, 71·15; H, 8·55%). Concentration of the aqueous alkaline phase, acidification, and isolation of the product with ether, and crystallisation from benzene, gave " acid A " (IV), m. p. 186° (Found: C, 69·9; H, 7·20. Calc. for $C_{12}H_{14}O_3$: C, 69·9; H, 6·85%). The *methyl ester*, prepared with diazomethane, had n_D^{22} 1·5325 (Found: C, 70·55; H, 7·4. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%).

Oxidation of the Glycol (III) *to " Acid A ".*—To the glycol (3·08 g.) in acetone (50 ml.) was added, with stirring, a 2% solution of potassium permanganate in the same solvent (230 ml.) during 30 min. After removal of the manganese dioxide the acidic material was isolated in the usual way and crystallised from benzene, to give " acid A " (IV) identical with material isolated by the direct oxidation of anisoxide.

2 : 3-*Dihydro*-3-*hydroxy*-2 : 2 : 3-*trimethylbenzofuran*-5-*carboxylic Acid* (V).—(*a*) To " acid A " (228 mg.) in 1% aqueous sodium carbonate solution (25 ml.) was added 2% aqueous potassium permanganate solution (24·5 ml.) during 20 min. After removal of the manganese dioxide the alkaline solution was concentrated and the acidic material isolated with ether in the usual way. After being washed with ether the resultant solid crystallised from aqueous alcohol, to give the *hydroxy-acid* (V), m. p. 223·5—224·5°, $\lambda_{max.}$ 260 mμ (ε 12,900) (Found: C, 64·4; H, 6·15. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%).

(*b*) Anisoxide (4·0 g.) was heated on the steam-bath and 4% aqueous potassium permanganate (970 ml.) was added slowly. After 16 hr. the excess of potassium permanganate was destroyed with ethanol and, after cooling and concentration, the neutral material was extracted with ether. The alkaline solution was then carefully acidified at 0° and the product crystallised from aqueous alcohol, to give the hydroxy-acid described above.

Acidification of the alkaline oxidation mixture with an excess of hydrochloric acid gave, instead of the hydroxy-acid, " acid B " (IX), m. p. 214°, $\lambda_{max.}$ 240 (ε 24,600), 246 (ε 22,600), 272 (ε 7450), 316 (ε 6100), and 330 mμ (ε 6500) (Found: C, 70·15; H, 6·2. Calc. for $C_{12}H_{12}O_3$: C, 70·55; H, 5·9. Calc. for $C_{11}H_{10}O_3$: C, 69·5; H, 5·3%). The same substance may be obtained by boiling the hydroxy-acid with acetic acid.

Ozonolysis of " Acid B " (IX).—" Acid B " (IX) (148 mg.) in chloroform (10 ml.) was ozonised at 17° until the characteristic spectrum of the acid was replaced by new maxima at 255 and 325 mμ (10 min.). Decomposition of the ozonide with water and isolation of the acidic material in the usual way gave, after filtration in ether through a column of silica gel and crystallisation from benzene, " acid C " (VIII), identical with the acid obtained in the following experiment. In a parallel experiment steam-distillation of the ozonised solution gave formaldehyde (11%), isolated as the dimedone derivative.

Oxidation of " Acid B " (IX).—This was performed as described by Jackson and Short.[1] After crystallisation from benzene the product " acid C " (VIII) had m. p. 181·5—182·5°, $\lambda_{max.}$ 229 (ε 35,600), 251 (ε 9500), and 325 mμ (ε 4200) (Found: C, 64·15; H, 5·2. Calc. for $C_{11}H_{10}O_4$: C, 64·05; H, 4·85%).

Conversion of " Acid C " (VIII) *into the Hydroxy-acid* (V).—The acid (107 mg.) was refluxed for 4 hr. with a solution (25 ml.) of methylmagnesium iodide (prepared from 197 mg. of magnesium), after which the mixture was decomposed with ice-water and hydrochloric acid. Isolation of the product and its crystallisation from benzene gave the hydroxy-acid identical with the material previously described (Found: C, 65·3; H, 6·1%).

Conversion of " Acid B " (IX) *into " Acid A "* (IV).—" Acid B " (43 mg.) was hydrogenated in acetic acid (5 ml.) in the presence of platinum oxide. After the uptake of 1·02 mol. of hydrogen the product was isolated to give, after crystallisation from benzene, " acid A " (IV), identified by m. p., mixed m. p., and spectra.

Synthesis of Anisoxide.—2-Hydroxy-5-methyl*iso*butyrophenone (X), $\lambda_{max.}$ 217 (ε 17,200), 256 (ε 11,250), and 334 mμ (ε 3600), was prepared as described by von Auwers *et al.*[6] The

[6] von Auwers, Baum, and Lorenz, *J. prakt. Chem.*, 1927, **115**, 98; von Auwers, *Ber.*, 1914, **47**, 2334; cf. also von Auwers and Lämmerhirt, *Annalen*, 1920, **421**, 1.

XUM

3 : 5-dinitrobenzoate, crystallised from benzene–light petroleum, had m. p. (Kofler) 190—193° (Found: C, 58·1; H, 4·55; N, 7·2. $C_{18}H_{16}O_7N_2$ requires C, 58·05; H, 4·35; N, 7·5%). The butyrophenone (21 g.) in dry ether (50 ml.) was added with stirring to an ethereal solution (300 ml.) of methylmagnesium iodide prepared from methyl iodide (100 g.) and magnesium (12 g.). After decomposition the product was isolated with ether and washed with sodium hydrogen carbonate solution, and the phenolic material was then extracted with sodium hydroxide. After isolation in the usual way the phenolic material was fractionated, the material of b. p. 142—146°/25 mm. being collected. Vapour-phase chromatography showed this fraction to be homogeneous 2-(2-hydroxy-5-methylphenyl)-3-methylbutan-2-ol (XI). The *3 : 5-dinitrobenzoate*, after crystallisation from aqueous methanol, had m. p. 116—117° (Found: C, 58·5; H, 5·4; N, 7·6. $C_{19}H_{20}O_7N_2$ requires C, 58·75; H, 5·2; N, 7·2%).

The alcohol (10·3 g.) was added to a solution of 60% perchloric acid (310 ml.) in acetic acid (105 ml.) containing acetic anhydride (35·5 ml.). After being set aside for 16 hr. the mixture was poured into water, and the neutral material isolated in the usual way. This was fractionated and the fraction of b. p. 132—133°/25 mm. collected, to give *2 : 3-dihydro-2 : 2 : 3 : 5-tetramethylbenzofuran* (XII), n_D^{28} 1·5100, $\lambda_{max.}$ 228—230 (ε 5700) and 287 mμ (ε 3100) (Found: C, 81·6; H, 9·2. $C_{12}H_{16}O$ requires C, 81·75; H, 9·15%).

The dihydrobenzofuran (XII) (255 mg.) in acetic acid (5 ml.) was oxidised with a 0·1N-solution of chromic acid in acetic acid (50 ml.). After 3·5 hr. the uptake was equivalent to 6·25 atoms of oxygen, no further uptake occurring during the next hour. Reduction of the excess of oxidant with sodium metabisulphite and isolation of the product in the usual way gave " acid C " (VIII), identical with the material obtained by oxidation of anisoxide.

Oxidation of the Dihydrobenzofuran (XII) *to " Acid B "* (IX).—The dihydrobenzofuran (163 mg.) was heated on the steam-bath and a 4% solution of potassium permanganate (30 ml.) was added slowly. After 8·5 hr. the mixture was cooled, excess of oxidant destroyed with sulphur dioxide, and the product isolated in the usual way. After crystallisation from chloroform–light petroleum " acid B " (IX) was obtained, identical in every respect with the material from the oxidation of anisoxide. Its identity was confirmed by hydrogenation with palladised charcoal in ethyl acetate to " acid A " (IV).

2 : 3-Dihydro-2 : 2 : 3-trimethyl-5-propionylbenzofuran (VII).—" Acid A " (IV) (2·15 g.) was suspended in benzene (6 ml.), oxalyl chloride (4·5 ml.) added, and the mixture set aside overnight. Excess of oxalyl chloride was removed from the now homogeneous solution by evaporation under reduced pressure, and the product dissolved in benzene (7 ml.) and added to a solution of diazoethane (1 g.) in ether (700 ml.). After 2 hr. the solution was evaporated to dryness, and the residual oil taken up in chloroform, shaken for 5 min. with 60% hydriodic acid (2 ml.), washed with aqueous sodium thiosulphate and saturated aqueous sodium hydrogen carbonate, and recovered. This red oil was dissolved in acetic acid and shaken with zinc dust for 1 hr. The product, isolated in the usual way, showed an infrared band at 1715 $cm.^{-1}$ due to a small amount of the ethyl ester of " acid A ". This was removed by dissolving the product in 3 : 7 aqueous dioxan (120 ml.), adding N-sodium hydroxide (20 ml.), and setting the whole aside for 40 hr. Isolation of the neutral material in the usual way and distillation gave *2 : 3-dihydro-2 : 2 : 3-trimethyl-5-propionylbenzofuran* (VII), b. p. 128—132°/0·4 mm., n_D^{29} 1·5363 (Found: C, 76·7; H, 8·4. $C_{14}H_{18}O_2$ requires C, 77·05; H, 8·3%). The *semicarbazone*, crystallised from chloroform–light petroleum, had m. p. (Kofler) 179—180° (Found: N, 15·6. $C_{15}H_{21}O_2N_3$ requires N, 15·25%). The ketone (VII) (590 mg.) in 1 : 1 aqueous methanol (60 ml.) containing potassium borohydride was set aside overnight. Isolation of the product gave after distillation (bath-temperature 180°) at 0·5 mm. the *2 : 3-dihydro-5-1′-hydroxypropyl-2 : 2 : 3-trimethylbenzofuran* (VI), n_D^{25} 1·5223, $\lambda_{max.}$ 231 (ε 5850) and 284 (ε 2440) mμ (Found: C, 76·35; H, 8·95. $C_{14}H_{20}O_2$ requires C, 76·3; H, 9·15%).

Dehydration of the Alcohol (VI) *to Anisoxide* (II).—(*a*) The alcohol (200 mg.) was distilled under reduced pressure from a small crystal of iodine. The product (23 mg.) was filtered in light petroleum solution through a column of alumina (Grade III; 700 mg.). Sublimation of the product gave a colourless oil which crystallised, then having m. p. 34—37° (Kofler) undepressed on admixture with authentic anisoxide.

(*b*) Optimum conditions were determined in preliminary experiments taking advantage of the maximum in the ultraviolet spectrum at 265 mμ. The alcohol (100 mg.) in ethanol (100 ml.) was treated with 6N-hydrochloric acid (70 drops), then refluxed for 20 min. The product was isolated with chloroform after neutralisation of the acid with sodium hydrogen carbonate.

XUM

After evaporation of the chloroform the residual oil (90 mg.) was filtered in light petroleum (b. p. 60—80°) through alumina (Grade III). Crystallisation of the product gave anisoxide (20 mg.) identified by m. p., mixed m. p., and infrared (chloroform solution) and ultraviolet spectra.

We thank the Government Grants Committee of the Royal Society and Imperial Chemical Industries Limited for financial assistance. One of us (A. B.) acknowledges the award by the University of Glasgow of an I.C.I. Fellowship; and another (G. A. M.) the receipt of a D.S.I.R. Maintenance Grant.

THE UNIVERSITY, GLASGOW, W.2.
IMPERIAL COLLEGE, LONDON, S.W.7. [*Received, June 23rd,* 1958.]

---

892. *The Generalised Diaxial ⟶ Diequatorial Rearrangement.*

By D. H. R. BARTON and J. F. KING.

The acetate, benzoate, and substituted benzoate esters of 2β-halogenocholestane-3α-ol have been shown to rearrange when heated, to give the corresponding 3β-halogenocholestan-2α-yl esters. The rates of these reactions have been determined and the kinetics shown to be of the first order. The equilibrium positions in these systems have been determined and proved to favour greatly the diequatorial compounds. The general scope and mechanism of such rearrangements are discussed.

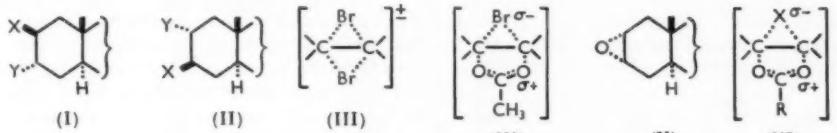
THE mutarotation of " ordinary " cholestene dibromide to a more stable isomer [1] has been shown to involve rearrangement of the diaxial 5α : 6β-dibromide to the diequatorial 5β : 6α-isomer.[2] Other examples of the diaxial–diequatorial rearrangement are provided by 2β : 3α-dibromocholestane (I; X = Y = Br) which, when heated,[3] rearranges to 2α : 3β-compound (II; X = Y = Br),[4,5] and by 3α : 4β-dibromocholestane which behaves similarly.[5] That this behaviour of 1 : 2-dibromides is a general reaction has been argued elsewhere,[6] notwithstanding opinions to the contrary.[7] The related thermal rearrangements of 2β-bromo-3α-chloro- (I; X = Br, Y = Cl) and of 3α-bromo-2β-chloro-cholestane (I; X = Cl, Y = Br) afford the isomers (II; X = Br, Y = Cl, and *vice versa*, respectively).[5] Thus the rearrangements proceed in such a way as to retain each halogen substituent on the same side of the molecule. In suitable compounds the dibromide rearrangement can be shown to afford an equilibrium mixture (of the diaxial and diequatorial isomers) which can be approached from either side.[8] All these, and other, facts are in agreement with a mechanism for the reaction [9] which is intramolecular and proceeds through a transition state as in (III).

It seemed to us *ab origine* that diaxial–diequatorial dihalide rearrangements might be merely the prototype of a whole family of rearrangements of the type (I) ⟶ (II). The present paper provides evidence that this is indeed the case.

Since the transition state (III) for the dibromide rearrangement is regarded as having polar character,[9] it seemed probable that if X in (I) could be made relatively electronegative and Y relatively electropositive then rearrangement should occur more readily. Studies were initiated, therefore, with 3α-acetoxy-2β-bromocholestane (I; X = Br, Y = OAc), for in the hypothetical transition state (IV) the charges should be accommodated as

[1] Mauthner and Suida, *Monatsh.*, 1894, **15**, 91; Mauthner, *ibid.*, 1906, **27**, 421.
[2] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066.
[3] Hattori and Kawasaki, *J. Pharm. Soc. Japan*, 1937, **57**, 115, 588.
[4] Barton and Rosenfelder, *J.*, 1951, 1048.
[5] Alt and Barton, *J.*, 1954, 4284.
[6] Barton, *Bull. Soc. chim. France*, 1956, 973.
[7] Cornubert, *ibid.*, p. 979.
[8] Barton and Head, *J.*, 1956, 932.
[9] Grob and Winstein, *Helv. Chim. Acta*, 1952, **35**, 782; see also Kwart and Weisfeld, *J. Amer. Chem. Soc.*, 1956, **78**, 635.

indicated. Heating the bromo-acetate (I; X = Br, Y = OAc) at 136° transformed it smoothly into an isomer, shown to be (II; X = Br, Y = OAc), on the basis of the following evidence. First, treatment with alkali gave 2α : 3α-epoxycholestane (V), indicating that the product was a *trans*-halogenohydrin [10] substituted at positions 2 and 3. Secondly, hydrogenolysis furnished the known [11] 2α-acetoxycholestane.



(I) (II) (III) (IV) (V) (VI)

Equilibration of the rearranged isomer (II; X = Br, Y = OAc) at 136° showed that the equilibrium mixture (I and II; X = Br, Y = OAc) contained 96 ± 3% of the latter (see Table 1). Similar equilibria were observed with all the other compounds studied (Table 1). Exact specification of the equilibrium points is not possible because of a slow

TABLE 1. *Rates of rearrangement of acyloxyhalogenocholestanes, at* 136° ± 1°.

Diaxial 2β : 3α-disubstituted cholestane		Half-life for rearrangement,	Average	10^4k	Diequatorial isomer (%) at	Rate relative to that of 3α-acetoxy-2β-bromocholestane
2β	3α	$t_{\frac{1}{2}}$ (min.)	$t_{\frac{1}{2}}$	(sec.$^{-1}$)	equilibrium	
Br	OAc	100, 117	108	1·07	96 ± 3	1·00
Br	OBz	77, 85	81	1·43	95 ± 2	1·33
Br	*p*-MeO·C_6H_4·CO_2	35·5, 27·5	32·5	3·55	97 ± 2	3·32
I	OAc	14·4, 15·0	14·7	8·04	96 ± 4	7·52
Cl	OAc	2460, 2500	2480	0·0466	93 ± 2	0·0435
Br	Br	71·5, 83·5	77·5	1·49	93 ± 1	1·39
Br	OAc *	29, 30	29·5	3·92	98 ± 2	—
Br	*p*-NO_2·C_6H_4·CO_2	105, 100	102·5	1·13	97 ± 3	0·29 †

* In phenanthrene solution. † Corrected for solvent effect.

more general decomposition observed with all the compounds. The acetate rearrangement was shown to follow good first-order kinetics proceeding at the rate indicated in Table 1.

Attention was next turned to the rearrangement of 3α-acetoxy-2β-chloro- and -2β-iodocholestane (I; X = Cl or I, Y = OAc, respectively). These compounds isomerised, following first-order kinetics (Table 1), to furnish 2α-acetoxy-3β-chloro- and -3β-iodocholestane (II; X = Cl and I, Y = OAc, respectively). The nature of these substances is based upon the exactly analogous behaviour of the corresponding bromide (see above), upon a comparison of $[M]_D$ data for these and all the other rearranged compounds reported in this paper (see Table 2), and upon the appropriate mixed m. p. relations (see Experimental section). The use of such comparisons has been justified in a similar series of diaxial and diequatorial isomers at the 2 : 3-positions in cholestane.[5] The constitutions of all the other diequatorial rearrangement products described in this paper are justified in a similar way.

It was of interest (see Table 1) that the rate of rearrangement of the chloro-acetate (I; X = Cl, Y = OAc) was about one twenty-fifth of that of the corresponding bromide, whereas the iodo-acetate (I; X = I, Y = OAc) rearranged about seven times as fast. The relative rates do not parallel the electronegativities of the halogens, which is what the order should be if only the capacity to bear negative charge, as in (IV), were important. The rates do follow, however, the relative polarisabilities of the halogens and ease of rupture

[10] Bartlett, *J. Amer. Chem. Soc.*, 1935, **57**, 224.
[11] Fürst and Plattner, *Helv. Chim. Acta*, 1949, **32**, 279.

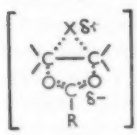
of the carbon–halogen bond. The transition state indicated as in (IV) implies that the reaction is exclusively intramolecular. Although this is not established rigidly by experiment, the conditions under which the reaction occurs are not such as to favour the incursion

TABLE 2. *Molecular rotations of* 2β : 3α- *and* 2α : 3β-*disubstituted cholestanes.*

2β : 3α-Isomer (I)		$[M_D]$ (in $CHCl_3$)	2α : 3β-Isomer (II)		$[M]_D$ (in $CHCl_3$)
2β	3α		2α	3β	
Br	Br	+403°	Br	Br	−159°
Br	OAc	+361	OAc	Br	−119
Cl	OAc	+297	OAc	Cl	−132
I	OAc	+507	OAc	I	−105
Br	Bz	+487	OBz	Br	−246
Br	*p*-MeO·C_6H_4·CO_2	+499	*p*-MeO·C_6H_4·CO_2	Br	−222
Br	*p*-NO_2·C_6H_4·CO_2	+497	*p*-NO_2·C_6H_4·CO_2	Br	−229
Br	*p*-C_6H_4Me·SO_3	+310	—	—	—

of a truly ionic mechanism. Similar considerations apply, of course, for the dibromide rearrangement [9] whose intramolecular nature is generally accepted.

A generalised transition state for halogenohydrin ester rearrangement, depicted in (VI), suggests that the rate of reaction should be increased by electron-accession from R and decreased by electron-withdrawal into R. Experiments were made with substituted benzoates in order to examine this idea. 2β-Bromocholestan-3α-yl benzoate (I; X = Br, Y = OBz) rearranged to the diequatorial isomer (II) with first-order kinetics (Table 1). The rate of reaction was about 30% greater than that for the acetate in agreement with the greater capacity of the benzoate to accommodate positive charge. The corresponding *p*-methoxy-derivative rearranged with first-order kinetics more than twice as fast (Table 1) as the unsubstituted benzoate in agreement with the electron-donating power of the *para*-methoxyl group. The *p*-nitrobenzoate (I) did not melt at 136°. Its rate of rearrangement was, therefore, determined in phenanthrene solution, the rate of rearrangement of the acetate being measured at the same time. Both reactions followed first-order kinetics but the rate for the acetate was four times as fast as for the pure molten ester. A similar marked solvent-dependence of rate has been observed previously with the cholestene dibromide.[9] Correcting the rearrangement rate of the *p*-nitrobenzoate for this solvent effect gave a rate about one-fifth of that of the unsubstituted benzoate. Electron-recession does, therefore, reduce the rate of the reaction. The relative rates of the benzoate rearrangements imply that an alternative representation of the transition state as in (VII) is improbable. The reason why simple polar considerations can be applied for variation of the electronic character of the benzoate, but not for variation in the nature of the halogen, is presumably that making and breaking of the partial covalent bond with respect to positions 2 and 3 remains the same for all the benzoates but varies for the various halogeno-acetate rearrangements. In principle it should be possible to test this idea by studying a diester rearrangement of the type (I) ⟶ (II) where X = Y = substituted benzoate, one ester having an electropositive substituent and the other an electronegative substituent.



(VII)

For comparison the rearrangement of the dibromide (I; X = Y = Br) was followed kinetically (Table 1). At 136° the reaction followed first-order kinetics at a rate slightly faster than that for the bromo-acetate (I; X = Br, Y = OAc).

The halogenohydrin ester rearrangements described here illustrate a principle which may be of importance in preparative work. It is well known that the oxide from an olefin opens diaxially to place the oxygen atom specifically on one of the two (olefinic) carbons. By the sort of rearrangement described here this oxygen can, in effect, be transferred from the carbon atom favoured by the geometrical requirements of oxide opening to the other carbon atom.

XUM

We conclude that the mechanism of these rearrangements is intramolecular through a generalised transition state of type (VI). The driving force for the rearrangement is clearly of conformational origin; *i.e.*, the compressions of the diaxial compound are minimised by isomerisation to the diequatorial isomer.

Experimental

Rotations were determined for chloroform solutions at room temperature. Neutral alumina graded according to the Brockmann scale of activity was used in chromatography. Solutions for chromatography were made up in light petroleum (b. p. 40—60°). Rearrangements were carried out in an atmosphere of oxygen-free nitrogen.

Rearrangement Procedure.—The samples were rearranged in a test-tube heated by vapour of a refluxing liquid. The latter was in a 1 l. flask fitted with condenser, thermometer, and Quickfit B24 neck. The test tube (20 × 2 cm.) was constructed with a Quickfit B24 male joint as the wall at the middle so that it fitted into the flask with the lower 5 cm. of the tube protruding into the bulb of the flask. The sample (30—60 mg.) was weighed into the tube, and a measured volume (2—3 ml.) of chloroform added. A portion of the solution was transferred to a polarimetric tube and the rotation determined. The polarimetric sample was quantitatively washed back into the test-tube with chloroform and the solvent carefully removed at <70° under reduced pressure. The test-tube was then inserted into the heating-flask and the rearrangement begun. The course of the reaction was followed by, at intervals, removing the test-tube, cooling it quickly to room temperature, determining the optical rotation (in $CHCl_3$ solution, as above), and returning the sample to the test-tube as before.

Ethylbenzene, which gave a temperature of 136° ± 1°, was used as the heating liquid in all kinetic experiments and for the determination of the positions of equilibria for the acetate derivatives and for the dibromides. Phenetole (b. p. 169° ± 1°) was used in the determination of the equilibrium positions in the other systems. The equilibrium points were approached from both the more stable (diequatorial) and the less stable (diaxial) isomers in every case.

2β-*Bromocholestan-3α-yl Acetate.*—Prepared according to Alt and Barton,[5] this was dimorphous, having m. p. 115—118° and 139—143°, $[\alpha]_D$ +70° (*c* 2·00). Alt and Barton [5] give m. p. 120—122°, $[\alpha]_D$ +71°.

2β-*Chlorocholestan-3α-yl Acetate.*—Prepared according to Alt and Barton,[5] this had m. p. 131—132°, $[\alpha]_D$ +64° (*c* 2·05) {lit.,[5] m. p. 128—130°, $[\alpha]_D$ +68°}.

2β-*Bromocholestan-3α-yl Benzoate.*—2β-Bromocholestan-3α-ol (600 mg.) in dry pyridine (5 ml.) was treated with benzoyl chloride (0·65 ml.) and left overnight at room temperature. It was then poured into water, set aside for 1 hr., and extracted with ether. The extract, after filtering through a column of alumina (Grade III), was evaporated and the residue crystallised four times from acetone, to give 2β-*bromocholestan-3α-yl benzoate*, as fine needles, m. p. 98—101°, $[\alpha]_D$ +85° (*c* 1·85) (Found: C, 71·4; H, 8·9; Br, 14·55. $C_{34}H_{51}O_2Br$ requires C, 71·4; H, 9·0; Br, 14·0%).

2β-*Bromocholestan-3α-yl* p-*Anisate.*—2β-Bromocholestan-3α-ol (800 mg.) was dissolved in dry pyridine (5 ml.). *p*-Anisoyl chloride (0·9 ml.) was added and the mixture treated as in the benzoylation (above). After three crystallisations from acetone, 2β-*bromocholestan-3α-yl* p-*anisate* was obtained as fine needles, m. p. 136—138°, $[\alpha]_D$ +83·1 (*c* 2·00) (Found: C, 70·0; H, 8·6; Br, 13·3. $C_{35}H_{53}O_3Br$ requires C, 69·8; H, 8·9; Br, 13·3%).

2β-*Bromocholestan-3α-yl* p-*Nitrobenzoate.*—2β-Bromocholestan-3α-ol (600 mg.) was added to a cold solution of toluene-*p*-sulphonyl chloride [12] (500 mg.) and *p*-nitrobenzoic acid (250 mg.) in pyridine (5 ml.). The mixture was left in an ice-bath for 2 hr., then poured into water and extracted with ether. The material from the extract was chromatographed on Grade III alumina. Elution with benzene gave 2β-*bromocholestan-3α-yl* p-*nitrobenzoate* (620 mg.) which, after four crystallisations from chloroform–acetone, had m. p. (fine needles) 198—200°, $[\alpha]_D$ +81° (*c* 2·1) (Found: C, 66·6; H, 8·1; N, 2·2; Br, 13·6. $C_{34}H_{50}O_4NBr$ requires C, 66·2; H, 8·2; N, 2·3; Br, 12·95%).

2β-*Bromocholestan-3α-yl Toluene*-p-*sulphonate.*—Toluene-*p*-sulphonyl chloride (500 mg.) was added to 2β-bromocholestan-3α-ol (400 mg.) in dry pyridine (5 ml.), and the mixture left for 4 days at room temperature. The mixture was poured into water and extracted with ether and the extracted material crystallised four times from acetone, to give 2β-*bromocholestan-3α-yl*

[12] Brewster and Ciatti, *J. Amer. Chem. Soc.*, 1955, **77**, 6214.

XUM

toluene-p-*sulphonate*, m. p. 168—170°, $[\alpha]_D$ +49° (*c* 1·75) (Found: C, 65·6; H, 8·6; Br, 13·35; S, 4·8. $C_{34}H_{53}O_3BrS$ requires C, 65·7; H, 8·6; Br, 12·85; S, 5·2%).

2β-*Iodocholestan*-3α-*ol*.—2α : 3α-Epoxycholestane (630 mg.) in chloroform (30 ml.) was shaken for 3 min. with a 55% aqueous solution of hydriodic acid [2] (12 ml.). The chloroform layer was washed quickly with dilute sodium sulphite solution, and the solvent removed under reduced pressure. The residue was crystallised from ether–methanol and acetone–methanol, to give 2β-*iodocholestan*-3α-*ol*, m. p. 132—133°, $[\alpha]_D$ +53° (*c* 2·0) (Found: C, 62·8; H, 9·4; I, 24·5. $C_{27}H_{47}OI$ requires C, 63·0; H, 9·2; I, 24·65%). 2β-*Iodocholestan*-3α-*yl acetate* was prepared by dissolving the iodohydrin in pyridine, adding excess of acetic anhydride, and allowing the mixture to remain overnight at room temperature. After four crystallisations from acetone–methanol the acetate melted at 131—133° and had $[\alpha]_D$ +91° (*c* 2·25) (Found: C, 62·6; H, 8·8. $C_{29}H_{49}O_2I$ requires C, 62·6; H, 8·9%).

Isolation of the Rearranged Halogeno-esters.—Chromatography of the products of thermal rearrangement on Grade I alumina (elution with 1 : 4 benzene–light petroleum) was followed by crystallisation from acetone–methanol. In this way were obtained: 3β-*Bromocholestan*-2α-*yl acetate*, m. p. 118—119°, $[\alpha]_D$ −22° (*c* 2·00) (Found: C, 68·6; H, 9·7; Br, 16·2. $C_{29}H_{49}O_2Br$ requires C, 68·35; H, 9·7; Br, 15·7%). 3β-*Bromocholestan*-2α-*yl benzoate*, m. p. 112—114°, $[\alpha]_D$ −43° (*c* 1·40) (Found: C, 71·4; H, 9·1; Br, 14·1. $C_{34}H_{51}O_2Br$ requires C, 71·4; H, 9·0; Br, 13·95%). 3β-*Bromocholestan*-2α-*yl* p-*anisate*, m. p. 114—115°, $[\alpha]_D$ −37° (*c* 2·25) (Found: C, 69·7; H, 9·0. $C_{35}H_{53}O_3Br$ requires C, 69·8; H, 8·9%). 3β-*Iodocholestan*-2α-*yl acetate*, m. p. 88—92°, $[\alpha]_D$ −19° (*c* 1·6) (Found: C, 62·9; H, 9·1; I, 23·1. $C_{29}H_{49}O_2I$ requires C, 62·6; H, 8·9; I, 22·8%). 3β-*Chlorocholestan*-2α-*yl acetate*, m. p. 138°, $[\alpha]_D$ −28° (*c* 1·95) (Found: C, 75·1; H, 10·3; Cl, 7·4. $C_{29}H_{49}O_2Cl$ requires C, 74·9; H, 10·6; Cl, 7·6%).

3β-*Bromocholestan*-2α-*yl* p-*Nitrobenzoate*.—2β-Bromocholestan-3α-yl *p*-nitrobenzoate (see above) (160 mg.) and phenanthrene (480 mg.) were heated (in four lots) until rearrangement was complete ($[\alpha]_D$). The product was chromatographed on Grade I alumina. After exhaustive elution with light petroleum and light petroleum–benzene (4 : 1) to remove the phenanthrene, elution with benzene gave 3β-*bromocholestan*-2α-*yl* p-*nitrobenzoate* which, after four crystallisations from acetone–methanol, had m. p. 158—159°, $[\alpha]_D$ −37° (*c* 1·85) (Found: C, 66·2; H, 8·1; N, 2·25; Br, 12·4. $C_{34}H_{50}O_4NBr$ requires C, 66·2; H, 8·2; N, 2·3; Br, 12·95%).

Hydrogenolysis of 3β-*Bromocholestan*-2α-*yl Acetate*.—This acetate (101 mg.) was hydrogenated for 8 hr. with prehydrogenated 10% palladium–charcoal (100 mg.) in ethanol (5 ml.) containing anhydrous sodium acetate (1 g.). The product, after three crystallisations from chloroform–methanol, was by m. p., mixed m. p., $[\alpha]_D$, and infrared spectrum identical with authentic cholestan-2α-yl acetate prepared by the method of Fürst and Plattner.[11]

Treatment of 3β-*Bromocholestan*-2α-*yl Acetate with Alkali* (*with* V. V. Kane).—3β-Bromocholestan-2α-yl acetate (75 mg.) was refluxed for 1½ hr. with 5% methanolic potassium hydroxide (10 ml.). Crystallisation of the product from ether–methanol gave 2α : 3α-epoxycholestane, identified by m. p., mixed m. p., and $[\alpha]_D$.

Tests for Isomorphism.—The following compounds were used: (1) 3β-bromocholestan-2α-yl acetate, (2) 3β-chlorocholestan-2α-yl acetate, (3) 3β-iodocholestan-2α-yl acetate, and (4) 2β-bromocholestan-3α-yl acetate. Nos. 1—3 are diequatorial, no. 4 is diaxial. The m. p. of a specimen of the lower-melting component of the mixture was always taken at the same time as that of the mixture. Mixed m. p.s were as follows: Diequatorial pairs (no depressions): (1) + (2) 122—133°; (1) + (3) 84—105°; (2) + (3) 84—110°. Diaxial–diequatorial pairs (depressed): (1) + (4) 95—120°; (2) + (4) 107—112°; (3) + (4) 77—120°.

We thank the Government Grants Committee of the Royal Society and Imperial Chemical Industries Limited for financial assistance. One of us (J. F. K.) acknowledges with gratitude the award of a Beaverbrook Overseas Scholarship.

Imperial College, London, S.W.7. [*Received, July 8th*, 1958.]

XUM

893. *Homolytic Aromatic Substitution. Part XVI.*[1] *Relative Rates of* p-*Bromophenylation of Nitrobenzene and* p-*Nitrophenylation of Bromobenzene. Derivation and Discussion of Partial Rate Factors.*

By Chang Shih, D. H. Hey, and Gareth H. Williams.

The determination, by means of competitive experiments, of the relative rates of *p*-bromophenylation of nitrobenzene and *p*-nitrophenylation of bromobenzene is reported. Partial rate factors for the arylation with various radicals of nitrobenzene, chlorobenzene, and bromobenzene are derived and discussed from the point of view of the polarity of the attacking free radicals. The validity of the competitive method is also discussed.

In Parts XIV [2] and XV [1] the influence of the polarised radicals on the ratios of isomers obtained in the *p*-bromophenylation and *p*-chlorophenylation of nitrobenzene, and the *p*-nitrophenylation of chlorobenzene and bromobenzene was investigated. The corresponding effect of radical polarisation on the relative rates of arylation of nitrobenzene and chlorobenzene, with use of *p*-chlorophenyl radicals, was reported in Part IX.[3] Further work on this aspect, namely, the measurement of the relative rates of *p*-bromophenylation of nitrobenzene and *p*-nitrophenylation of bromobenzene, is now reported. This, together with the results reported in Parts IX,[3] XIV,[2] and XV,[1] makes possible the calculation of partial rate factors for a number of new arylation reactions, in terms of which the influence of the polarising groups in the radicals may be preliminarily discussed. Further extensions of this work, with a greater variety of both radicals and substrates, will be reported in future publications.

The relative rate ratios ${}^{PhNO_2}_{PhH}K$ and ${}^{PhNO_2}_{PhBr}K$ have been determined for *p*-bromophenylation and *p*-nitrophenylation respectively, Augood, Hey, and Williams's competitive technique [4] being used. The former measurement gives the relative rate of *p*-bromophenylation of nitrobenzene directly, and the relative rate of *p*-nitrophenylation of bromobenzene can be obtained from the latter measurement, in conjuncton with the value of ${}^{PhNO_2}_{PhH}K$ for *p*-nitrophenylation obtained by Hambling, Hey, and Williams.[5]

Experimental

Preparation of Reagents.—Benzene, bromobenzene, and nitrobenzene were purified as described in Parts II [4] and IV.[6] *p*-Bromobenzoyl peroxide (m. p. 142°, decomp.) and *p*-nitrobenzoyl peroxide (m. p. 155°, decomp.) were prepared from *p*-bromobenzoyl chloride and *p*-nitrobenzoyl chloride respectively by Hey and Walker's method.[7]

Determination of ${}^{PhNO_2}_{PhH}K$ *for* p-*Bromophenylation.*—Experiments 1 and 2 were carried out with *p*-bromobenzoyl peroxide (6 g.) in an equimolar mixture (200 ml.) of benzene and nitrobenzene. The reactions were allowed to proceed in a thermostat at 80° for 72 hr. The mixed diaryls from the reaction mixtures were isolated by standard methods (cf. Part II [4]), and the composition of these mixtures determined volumetrically by reduction of the nitrodiaryls with titanous chloride, as described in Part II.[4] In the final distillation, fore-runs were collected, consisting of mixed fractions containing the last traces of nitrobenzene (the higher-boiling solvent) and the first traces of 4-bromodiphenyl (the lowest-boiling diaryl product). The fore-runs were analysed by the micro-Carius method, and a correction in terms of bromodiphenyl was applied to the yield and composition of the diaryl fraction. Fractions taken immediately

[1] Part XV, Chang Shih, Hey, and Williams, *J.*, 1958, 2600.
[2] *Idem, ibid.*, p. 1885.
[3] Cadogan, Hey, and Williams, *J.*, 1955, 1425.
[4] Augood, Hey, and Williams, *J.*, 1952, 2094.
[5] Hambling, Hey, and Williams, to be published.
[6] Augood, Cadogan, Hey, and Williams, *J.*, 1953, 3412.
[7] Hey and Walker, *J.*, 1948, 2213.

XUM

before the fore-run consisted entirely of nitrobenzene, showing that neither the fore-run nor the diaryl fraction was contaminated with benzene, and that the whole of the 4-bromodiphenyl formed was contained in the diaryl fraction and the fore-run. The absence of bromonitrodiphenyls from the fore-runs is inferred because they did not distil until a temperature 50° above that at which the fore-runs were collected had been reached. No significant amount of high-boiling residue was left after the distillation. The results are given in Table 1.

TABLE 1.

Expts.	1	2
Diaryl fraction (g.) (b. p. 55—135°/0·1 mm.)	3·096	3·075
Nitrodiaryls (%) in diaryl fraction	67·99	68·31
Fore-run (g.) (b. p. 35—55°/0·1 mm.)	0·998	1·049
Bromodiphenyl in fore-run (g.)	0	0·037
Corr. wt. of diaryl fraction (g.)	3·096	3·112
Nitrodiaryls, corr. (%)	67·99	67·50
$^{PhNO_2}_{PhH}K$	1·78	1·74
p-Br·C_6H_4·CO_2H (g.) (free and from hydrolysis of esters)	3·22	3·19
(p-Br·C_6H_4·CO·O)$_2$ accounted for (%)	82·0	82·5

Hence, $^{PhNO_2}_{PhH}K = 1·76$

Determination of $^{PhNO_2}_{PhBr}K$ *for* p-*Nitrophenylation.*—Experiments 3 and 4 were carried out with p-nitrobenzoyl peroxide (6 g.) in exactly the same way as above, except that bromobenzene was substituted for benzene, and isolation and analysis of the diaryl fraction were carried out by the standard procedure. Fore-runs were taken and analysed for nitrobenzene by titanous chloride titration. They were found to consist entirely of nitrobenzene, and hence no correction to the yield and composition of the diaryl fraction was necessary. The clean separation of the diaryl fraction from nitrobenzene, which was possible with these mixtures, was due to the considerable difference in b. p. between nitrobenzene and the bromonitrodiphenyls, which were the most volatile of the diaryl products. The absence of dinitrodiphenyls from the fore-runs is inferred because they did not distil until a temperature 80° above that at which the fore-runs were collected had been reached. Fractions taken immediately before the fore-runs consisted entirely of nitrobenzene. The amounts of high-boiling residue left after the distillation were negligible. The results are given in Table 2.

TABLE 2.

Expts.:	3	4
Diaryl fraction (g.) (b. p. 90—165°/0·2 mm.)	3·734	3·710
Dinitrodiphenyls (%) in diaryl fraction	35·09	35·86
Fore-run (g.) (b. p. 35—90°/0·2 mm.)	3·515	1·473
Bromonitrodiphenyls in fore-run (g.)	0·000	0·000
$^{PhNO_2}_{PhBr}K$	0·62	0·64
p-NO_2·C_6H_4·CO_2H (g.) (free and from hydrolysis of esters)	3·15	3·21
(p-NO_2·C_6H_4·CO·O)$_2$ accounted for (%)	83·0	84·0

Hence $^{PhNO_2}_{PhBr}K = 0·63$

DISCUSSION

The results of the above experiments on homolytic p-bromophenylation and p-nitrophenylation, in comparison with the corresponding figures for phenylation (Parts II [4] and IV [6]), are summarised in Table 3.

TABLE 3.

	Phenylation	p-Bromophenylation	p-Nitrophenylation	Decrease (%)
$^{PhNO_2}_{PhBr}K$	2·27	—	0·63	72
$^{PhNO_2}_{PhH}K$	4·00	1·76	—	56

The relative rates for p-bromophenylation and p-nitrophenylation are significantly lower than the corresponding relative rates for phenylation. Considering the properties

towards electrophilic substitution of the substrates used, these changes are in accord with the predictions of Cadogan, Hey, and Williams [3] for substitution by electrophilic radicals. Thus we conclude that bromo- and nitro-substituents, when present in the *para*-position of the aryl radicals, confer some measure of electrophilic character on these radicals. Moreover, the effect appears to be more marked in the case of the *p*-nitrophenyl radical than in that of *p*-bromophenyl. This is consistent with the known polar properties of the groups concerned, if it be assumed that the properties of the radicals are influenced by the permanent polarisation occasioned by the presence of the substituents. Thus both groups are known to cause such permanent polarisation of molecules containing them in the direction of electron-attraction by the substituent, the effect being greater in the case of the nitro-group.

From the above value of ${}^{PhNO_2}_{PhBr}K$ for *p*-nitrophenylation, taken in conjunction with the value [5] for the same reaction of ${}^{PhNO_2}_{PhH}K = 0{\cdot}94$, the rate of *p*-nitrophenylation of bromobenzene relative to benzene $\left({}^{PhBr}_{PhH}K\right)$ can be obtained, and is 1·49. This value, together with that of ${}^{PhNO_2}_{PhH}K$ for *p*-bromophenylation, and the results of Cadogan, Hey, and Williams [3] for *p*-chlorophenylation, can be used in conjunction with the relevant ratios of isomers, the determination of which was reported in Parts XIV and XV, to evaluate partial rate factors for a number of arylations. These results are given in Table 4, which also includes, for comparison, the values for partial rate factors for the phenylation of nitrobenzene, chlorobenzene, and bromobenzene previously reported.[1,2,4,6]

TABLE 4. *Partial rate factors for homolytic arylation.*

Radical	Substrate PhX	${}^{PhX}_{PhH}K$	F_o	F_m	F_p
p-Br·C_6H_4·	$PhNO_2$	1·8	3·1	0·7	2·9
p-Cl·C_6H_4·	$PhNO_2$	1·5	2·7	0·6	2·5
Ph·	$PhNO_2$ *	4·0	7·5	1·2	6·6
Ph·	PhBr	1·7	2·6	1·7	1·8
p-NO_2·C_6H_4·	PhBr	1·5	2·7	1·1	1·3
p-NO_2·C_6H_4·	PhCl	1·2	2·1	0·8	1·1
Ph·	PhCl *	1·4	2·2	1·4	1·6

* The values quoted here are somewhat different from those previously reported [4,6] since the present values were calculated by using the modified ratios of isomers obtained in the phenylation of nitrobenzene and chlorobenzene, the redetermination of which was reported in Parts XIV [2] and XV.[1]

In the arylation of nitrobenzene it is apparent from Table 4 that all three nuclear positions are considerably less reactive towards attack by *p*-chloro- and *p*-bromo-phenyl than by phenyl radicals, and that there is little difference in properties between *p*-bromo- and *p*-chloro-phenyl radicals. Moreover, the decrease in reactivity occasioned by the change from phenyl to *p*-halogenophenyl radicals is more marked in the *ortho*- and *para*- than in the *meta*-position of nitrobenzene. This is consistent with the known facts concerning electrophilic substitution in nitrobenzene, wherein the nitro-group, by virtue of its polar nature, deactivates the nucleus as a whole, but the *meta*-position less than the *ortho*- and *para*-positions. Thus, when homolytic substitution by electrophilic radicals takes place, it is to be expected that the reactivities of the nuclear positions should be decreased relative to the corresponding reactivities for substitution by neutral radicals in the order $o, p > m$. The foregoing interpretation of the results obtained with *p*-chloro- and *p*-bromo-phenyl radicals depends on the assumption that free-radical reactions are subject to polar influences, and that the *p*-halogenophenyl radicals are electrophilic when compared with phenyl radicals. This is undoubtedly due to the electron-attracting properties of the halogens, which permanently polarise the radicals containing them in the direction of withdrawal of electrons from the reactive position, which formally carries the unpaired

[6] Augood, Hey, and Williams, *J.*, 1953, 44.

electron. This position therefore suffers an electronic deficiency and the radical would be expected to react most readily, other things being equal, at positions of high electron density. It may be concluded, therefore, that the properties of free radicals are to some degree determined by any permanent polarisation which they may owe to their molecular constitution. It is not clear to what extent, if at all, the properties of radicals are influenced by the time-variable effects of any substituents they may contain on the polarisability of the radicals. The small magnitude of the observed effects indicates that the part played by polar factors in determining the properties of radicals is relatively minor, for even when substitution takes place in such an extensively polarised compound as nitrobenzene, the substitution process is very much more akin to homolytic substitution by neutral free radicals than to electrophilic substitution. It could hardly be expected to be otherwise, since it must always involve entities containing odd numbers of electrons (free radicals by definition), and the pairing of electrons to form covalent bonds must always be the fundamental influence on the behaviour of these reagents.

In the arylation of the halogenobenzenes, it is clear from Table 4 that the aromatic nuclei of these compounds are less reactive towards substitution by the electrophilic *p*-nitrophenyl radicals than by non-polarised phenyl radicals. This is consistent with the deactivating influence of the halogens in electrophilic substitution. However, as a result of the combination of polar influences displayed by the halogens ($-I + T$ effects) in electrophilic substitution, it is the *meta*-position which suffers the greatest deactivation. Table 4 shows that this property is also displayed in the behaviour of the halogenobenzenes towards homolytic substitution by electrophilic radicals, since the decrease in reactivity occasioned by the change from phenyl to *p*-nitrophenyl radicals is most marked in the *meta*-positions. This indicates that the polar factors which influence homolytic substitution by polarised free radicals are substantially the same as those which are known to operate in heterolytic substitution.

It is therefore clear that the present results reported and those in Parts XIV [2] and XV [1] are in accord with the general theory of the behaviour of polarised radicals as enunciated by Dannley and Sternfeld,[9] and by Cadogan, Hey, and Williams,[3] and elaborated here. The present results, however, also demonstrate that polar influences play only a relatively small part in determining the course of homolytic reactions. It is, perhaps, an unfortunate consequence of this that the differences, especially in ratios of isomers, which are indicative of the operation of polar influences, are also small and are often only just outside the experimental errors. For this reason it is the more desirable to examine as wide a variety of both radicals and substrates as possible. Further investigation on these lines has therefore been undertaken, and the results will be reported in due course.

The competitive method, whose use to obtain relative rates of homolytic arylation has been described in this and preceding papers, has recently been discussed by Lynch and Pausacker.[10] From reactions of some aroyl peroxides with benzene, chlorobenzene, and naphthalene, they isolated considerable quantities of high-boiling resins which they consider to contain derivatives of the isomeric quaterphenyls together with some esters formed by benzoyloxylation of the various compounds present. The quaterphenyls are considered to arise by dimerisation of the addition complex formed between the aryl radical and the aromatic substrate in the first stage of the arylation process. The differential removal, by this and other processes giving rise to the resins, of the various diaryl products occurring in the reaction mixtures obtained in competitive experiments is considered by them to invalidate the results obtained from competitive reactions in which benzoyl peroxide is used as the source of phenyl radicals. A similar view has been expressed by Walling.[11] This criticism would be serious if it could correctly be applied to the results under discussion. It is therefore necessary to examine its validity, if it be accepted that Lynch and Pausacker's

[9] Dannley and Sternfeld, *J. Amer. Chem. Soc.*, 1954, **76**, 4543.
[10] Lynch and Pausacker, *Austral. J. Chem.*, 1957, **10**, 40, 49, 165.
[11] Walling, " Free Radicals in Solution," John Wiley & Co. Inc., New York, 1957, p. 485.

conclusions are correct and are founded on a sound experimental basis. In this connection, it is relevant that some of their results on the reaction of benzoyl peroxide with naphthalene have been shown by Davies, Hey, and Williams [12] to be in error.

According to Lynch and Pausacker, the results of any competitive reaction in which high-boiling resins are obtained are subject to some uncertainty, owing to the possible differential removal of diaryl products. However, as has been pointed out by Augood and Williams [13] resins are formed only when the substrate consists entirely of relatively unreactive (" slow ") solvents such as benzene, pyridine, the alkylbenzenes, or the halogenobenzenes. If the substrate consists of " fast " solvents (*e.g.*, nitrobenzene or diphenyl), either alone or mixed with slow solvents, very little resin is obtained. This conclusion is amply confirmed by the results reported in this series. If only negligible quantities of resin are formed, no significant differential removal of the diaryl products can have taken place, and Lynch and Pausacker's criticism is inapplicable. All the relative rates reported in this and earlier papers are based on competitive experiments in which the reference solvent, which forms one component of the solvent mixture, was nitrobenzene. Only very small quantities of resins were formed in these reactions, and consequently the results cannot be regarded as invalid. In some cases, pyridine was used as reference solvent in competitive experiments conducted for the purpose of confirming the results obtained by using nitrobenzene as reference solvent. In these reactions, resins were obtained when the substrate consisted exclusively of slow solvents, and because of the uncertainty thus introduced, these experiments have never been relied upon alone, but have always been supported by ones with nitrobenzene. Even so, the agreement between results obtained by the two methods has been good, and this suggests that the complications introduced by differential removal of products are, in most cases, not serious, and occasions greater confidence in the reliability of the results. This confidence is also increased by the considerable measure of agreement between the values of a number of relative rates obtained by various cyclic procedures involving competitive experiments with different pairs of solvents, as shown in Part II.[4] The competitive results, and the partial rate factors derived therefrom, have also been shown (Part III [8]) to give rise to predictions of the relative rates of arylation of polysubstituted benzenes which are substantially in agreement with experimentally determined values. The relative rates also agree with theoretical predictions based on the calculation of both atom localisation energies and free valency numbers (cf. Augood and Williams [13]). Thus there appears to be much evidence supporting the published values of these relative rates derived from competitive experiments. It has never been claimed that these figures are accurate to, say, $\pm 1\%$, and indeed, the theoretical interest of these quantities does not lie in such an accurate knowledge of them, but rather in their order of magnitude and in the way in which they vary from one compound to another. It is therefore concluded that, on the experimental evidence at present available, the values reported and the discussions based upon them are unaffected by Lynch and Pausacker's criticisms.

KING'S COLLEGE, STRAND, LONDON, W.C.2. [*Received, July 24th*, 1958.]

[12] Davies, Hey, and Williams, *J.*, 1958, 1878.
[13] Augood and Williams, *Chem. Reviews*, 1957, **57**, 123.

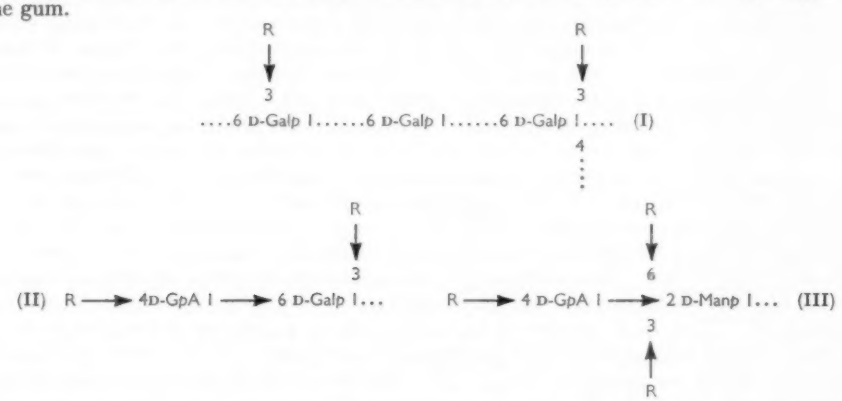
XUM

894. *Gum Ghatti (Indian Gum). Part III.*[1] *Neutral Oligosaccharides formed on Partial Acid Hydrolysis of the Gum.*

By G. O. Aspinall, (Mrs.) Barbara J. Auret, and E. L. Hirst.

Partial acid hydrolysis of the gum affords two homologous series of oligosaccharides together with small amounts of 3-*O*-β-D-galactopyranosyl-D-galactose and other disaccharides. The first three members of the series *O*-β-D-galactopyranosyl-[(1 → 6)-*O*-β-D-galactopyranosyl]$_n$-(1 → 6)-D-galactose (n = 0, 1, and 2) and the first four members of the series *O*-β-D-galactopyranosyl-[(1 → 6)-*O*-β-D-galactopyranosyl]$_n$-(1 → 3)-L-arabinose (n = 0, 1, 2, and 3) have been characterised. The significance of these results is discussed.

The results of previous structural studies on gum ghatti[1] can be summarised in the partial structures (I), (II), and (III). The gum contains chains of 1 : 6-linked β-D-galactopyranose residues (I) to which are attached either directly or through one or more 1 : 6-linked galactose residues the aldobiouronic acid units (II and III). The majority of the substituents R are single non-reducing L-arabofuranose end-groups. We now report an examination of the neutral oligosaccharides formed on partial acid hydrolysis of the gum.



The gum was partially hydrolysed by hot dilute sulphuric acid, and the mixture of neutral sugars formed was fractionated by chromatography on charcoal, followed where necessary by partition chromatography on cellulose, and the oligosaccharide fractions were examined. The main products were members of an homologous series of galactose-containing oligosaccharides. The first member was the disaccharide, 6-*O*-β-D-galactopyranosyl-D-galactose (IV; n = 0), whose structure was proved by the isolation of equimolecular proportions of 2 : 3 : 4 : 6-tetra- and 2 : 3 : 4-tri-*O*-methyl-D-galactose on hydrolysis of the methylated derivative. The presence of a β-glycosidic linkage was indicated by the low positive optical rotation ($[\alpha]_D$ +31°) of the disaccharide, which was similar to that recorded for the 1 : 6-linked galactobiose isolated from the partial acid hydrolysis of golden-apple gum[2] and markedly different from that reported for 6-*O*-α-D-galactopyranosyl-D-galactose, the major product of the acid-catalysed reversion of D-galactose.[3] The structure of the second member of the series, *O*-β-D-galactopyranosyl-(1 → 6)-*O*-β-D-galactopyranosyl-(1 → 6)-D-galactose (IV; n = 1), follows from the

[1] (*a*) Part I, *J.*, 1955, 1160; (*b*) Part II, *J.*, 1958, 221.
[2] Lindgren, *Acta Chem. Scand.*, 1957, **11**, 1365.
[3] Turton, Bebbington, Dixon, and Pacsu, *J. Amer. Chem. Soc.*, 1955, **77**, 2565.

isolation of 2 : 3 : 4 : 6-tetra- and 2 : 3 : 4-tri-*O*-methyl-D-galactose in the proportion of 1 : 2 on hydrolysis of the methylated trisaccharide. The optical rotation ($[\alpha]_D$ +20°) of the trisaccharide was consistent with the presence of two β-D-galactopyranosyl linkages. A third galactose-containing oligosaccharide was probably galactotetraose (IV; $n = 2$, as its optical rotation ($[\alpha]_D$ +14°) and its chromatographic mobility were consistent with the addition of another β-D-galactopyranosyl residue and since partial acid hydrolysis gave only one disaccharide, the 1 : 6-linked galactobiose.

(IV) D-Galp 1—$^{\beta}$[—6 D-Galp 1—$^{\beta}$]$_n$—6 D-Galp D-Galp 1—$^{\beta}$[—6 D-Galp 1—$^{\beta}$]$_n$—3 L-Ara (V)

A second series of oligosaccharides was isolated in smaller amount. These new oligosaccharides, which were all obtained crystalline, contained galactose residues and one arabinose residue per molecule. In each case the arabinose was at the reducing end of the molecule since reduction with potassium borohydride followed by hydrolysis of the derived glycitol gave only galactose. The first member of the series was 3-*O*-D-galactopyranosyl-L-arabinose (V; $n = 0$) since hydrolysis of the methylated disaccharide gave 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose and 2 : 4-di-*O*-methyl-L-arabinose, together with traces of 2 : 5-di-*O*-methyl-L-arabinose. If it is assumed that the reducing arabinose residue in the disaccharide is present in the pyranose form, the observed optical rotation {$[\alpha]_D$ +62° (equil.)} is only consistent with the presence of a β-D-galactopyranosyl linkage and may be compared with that observed for 3-*O*-α-D-galactopyranosyl-L-arabinose ($[\alpha]_D$ +152°), which has been isolated from the partial acid hydrolysis of *Acacia cyanophylla* gum [4] and as its methylated derivative from gum arabic.[5] The presence of an α-glycosidic linkage in the latter has recently been proved by its degradation to 2-*O*-α-D-galactopyranosylglycerol.[6] Preliminary evidence for the structure of the second member of the series was the detection of 3-*O*-β-galactopyranosylarabinose and 6-*O*-β-galactopyranosylgalactose on partial hydrolysis, and the mode of linkage of the sugars was proved by the isolation of 2 : 3 : 4 : 6-tetra-*O*-methyl- and 2 : 3 : 4-tri-*O*-methyl-D-galactose, and 2 : 4- and in small amount 2 : 5-di-*O*-methyl-L-arabinose from hydrolysis of the methylated trisaccharide. Since arabinose is present as the reducing residue it follows that the trisaccharide is *O*-β-D-galactopyranosyl-(1 ⟶ 6)-*O*-β-D-galactopyranosyl-(1 ⟶ 3)-L-arabinose (V; $n = 1$). The tetrasaccharide (V; $n = 2$) and pentasaccharide (V; $n = 3$) were established as members of the same homologous series by the following observations: (i) a plot of the R_M values [7] of the series, galactosylarabinose to tetragalactosylarabinose, against degree of polymerisation was a straight line; (ii) hydrolysis gave galactose and arabinose in the proportions of 2·8 : 1 and 3·7 : 1; (iii) chromatography of the products of partial acid hydrolysis showed only two disaccharides, 3-*O*-galactosylarabinose and 6-*O*-galactosylgalactose, together with arabinose, galactose, and higher oligosaccharides.

In addition to these major products of partial acid hydrolysis of the gum, very small quantities of other disaccharides were isolated. 3-*O*-β-D-Galactopyranosyl-D-galactose, previously characterised as a partial hydrolysis product of *Acacia pyanantha* gum,[8] golden-apple gum,[2] and of larch ε-galactan,[9] was identified as the crystalline sugar. A second minor component is tentatively believed to be an α-linked galactosylglucose. The structural significance of this disaccharide is not yet clear as glucose has not been detected previously as a constituent of the gum. Four arabinose-containing disaccharides were detected chromatographically, but in insufficient quantity for further study. Since the two disaccharides present in greatest amount in the mixture were chromatographically

[4] Charlson, Nunn, and Stephen, *J.*, 1955, 269.
[5] Smith, *J.*, 1939, 744.
[6] Charlson, Gorin, and Perlin, *Canad. J. Chem.*, 1957, **35**, 365.
[7] Bate-Smith and Westhall, *Biochem. Biophys. Acta*, 1950, **4**, 427.
[8] (*a*) Hirst and Perlin, *J.*, 1954, 2622; (*b*) Perlin, *Analyt. Chem.*, 1955, **27**, 396.
[9] Aspinall, Hirst, and Ramstad, *J.*, 1958, 593.

XUM

indistinguishable from the two reducing disaccharides, 3- and 4-*O*-β-L-arabopyranosyl-L-arabinose, formed by acid-catalysed reversion from L-arabinose,[10] it is not certain that these substances are true fragments of the original polysaccharide.

The isolation of the first homologous series (IV) of oligosaccharides from partial acid hydrolysis of gum ghatti was to be expected since the formation of 2 : 3 : 4-tri-*O*-methyl-D-galactose as the major product of hydrolysis of the methylated degraded gum[1b] indicated that chains of 1 : 6-linked D-galactopyranose residues (I) formed the backbone of the molecular structure of the gum. It is probable that 3-*O*-β-D-galactopyranosyl-D-galactose, isolated only in small amount, has structural significance and is not an artefact, since it is known that the major product of the acid-catalysed reversion of D-galactose is 6-*O*-α-D-galactopyranosyl-D-galactose[3] and no trace of such a disaccharide was found amongst the hydrolysis products of the gum. As a small amount of 2 : 4-di-*O*-methyl-D-galactose was isolated on hydrolysis of the methylated degraded gum,[1b] it is possible that the 1 : 3-linked galactobiose arises from a small degree of branching in the galactan backbone of the gum.

The isolation of the second homologous series (V) of oligosaccharides from gum ghatti points to a previously unsuspected structural feature, namely, the presence of L-arabinose residues in the backbone of the gum structure. Hitherto, structural investigations on plant gums have only shown arabinose residues, usually in the furanose form, to be present in the outer chains of the polysaccharides, and indeed, in gum ghatti the majority of arabinose residues are thus located. Here, the structural significance of 3-*O*-β-D-galactopyranosyl-L-arabinose as a fragment of gum ghatti may be contrasted with that of 3-*O*-α-D-galactopyranosyl-L-arabinose in *Acacia cyanophylla* gum[4] and gum arabic[5] where the disaccharide unit is removed under very mild conditions of hydrolysis and probably originates from the periphery of the gum molecule. Indications of the presence of arabinose residues in the more acid-resistant part of the gum molecule were obtained in earlier experiments.[1] Autohydrolysis of the gum resulted in cleavage of the more acid-labile linkages and a degraded gum was isolated which still contained a small proportion of arabinose residues,[1a] but such arabinose residues were not found in the methylated degraded gum.[1b] Further experiments now suggest that the majority of arabinose residues in the degraded gum are reducing groups terminating chains of 1 : 6-linked galactose residues.

When a sample of the degraded gum was partially hydrolysed with acid 3-*O*-β-D-galactopyranosylarabinose was easily detected by chromatography as one of the hydrolysis products. However, if the degraded gum was either oxidised with bromine water or treated with lime-water, and the product partially hydrolysed, only traces of 3-*O*-β-galactopyranosylarabinose were detectable. The arabinose residues in the degraded gum were therefore, either oxidised to arabonic acid residues or degraded with alkali, probably with the formation of saccharinic acids.[11] Since 1 : 3-linked carbohydrates are very susceptible to degradation by alkali, methylation of the degraded gum under alkaline conditions would easily result in loss of the reducing arabinose moiety. It is probable that the exposure of these reducing arabinose residues during the autohydrolysis results from the cleavage of acid-labile glycosidic linkages in the inner chains of the gum structure, and that in the original gum chains of 1 : 6-linked β-D-galactopyranose residues are joined through 1 : 3-linked L-arabinose residues as in (VI). Our earlier methylation studies[1b] showed that both 1 : 3-linked L-arabofuranose and L-arabopyranose residues were present in the gum, but it is probable that the formation of the degraded gum involves cleavage of arabofuranosyl linkages.

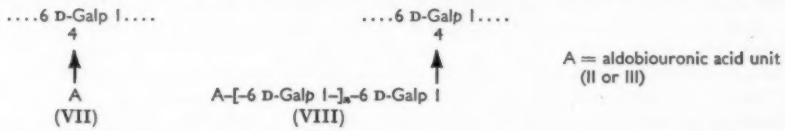
....6 D-Galp 1 ⟶ 6 D-Galp 1 ⟶ 3 L-Araf (or L-Arap) 1..... 6 D-Galp 1.... (VI)

The aldobiouronic acid units (II and III) in gum ghatti are present as side-chains and are probably linked to galactose through position 4, but in our earlier experiments it was

[10] Jones and Nicholson, *J.*, 1958, 27.
[11] Kenner, *Chem. and Ind.*, 1955, 727.

not possible to distinguish between direct attachment of these units to the backbone (VII) and attachment through one or more 1 : 6-linked galactose residues (VIII). Since the glycopyranosyluronic acid linkages in aldobiouronic acids are extremely resistant to acid hydrolysis, the isolation on partial hydrolysis of the gum of a neutral disaccharide containing a 1 : 4-linked galactose residue would only be expected if the aldobiouronic acid units were not directly linked to the backbone (VIII). The failure to detect such a disaccharide provides negative evidence in favour of direct attachment (VII). Experiments to obtain positive evidence for the mode of linkage of aldobiouronic acid units (II and III) to the galactan backbone are in progress.

D-Mannose residues in the gum are known to be present in the aldobiouronic acid unit (III). Since glucopyranosyluronic acids are resistant to acid hydrolysis it would only be expected that neutral mannose-containing disaccharides would be formed as products



of partial acid hydrolysis of the gum if some mannose residues were linked to neutral sugars only. The apparent absence of such neutral disaccharides in the partial hydrolysis products provides negative evidence for the occurrence of mannose residues linked only in aldobiouronic acid units (III). Since glucuronic acid is also linked to galactose in the gum there should be present a higher proportion of glucuronic acid than of mannose residues. Whereas previous results [1a] indicated the presence of glucuronic acid and mannose residues in the proportion of 1 : 1 in the original and also in the degraded gum, re-analysis of the degraded gum shows the proportion to be greater than 2 : 1.

Recent experiments on the ionophoresis of polysaccharides on glass-fibre paper [12] have indicated that gum ghatti is heterogeneous. Professor F. Smith (personal communication) informs us that the glass-fibre ionophoreses show gum ghatti to contain a major component and two minor components, one of which might be a pentosan. The results of methylation experiments [1b] suggested that the gum might contain one minor component since xylose residues present in the original gum [1a] were not found in the methylated polysaccharide, but we have not yet found evidence for a second minor component. Further experiments will be necessary before the nature of the heterogeneity of gum ghatti can be ascertained.

Experimental

Paper partition chromatography was carried out on Whatman No. 1 filter paper with the following solvent systems (v/v): (A) ethyl acetate–pyridine–water (10 : 4 : 3); (B) butan-1-ol–ethanol–water (4 : 1 : 5; upper layer); (C) butan-1-ol–ethanol–water (1 : 1 : 1); (D) ethyl acetate–acetic acid—formic acid–water (18 : 3 : 1 : 4). Optical rotations were observed at 18° ± 2°.

Partial Acid Hydrolysis of Gum Ghatti and Fractionation of Neutral Oligosaccharides.—Gum ghatti (100 g.) in water (1·95 l.) was heated to 100°, 4N-sulphuric acid (50 ml.) was added, and the solution was boiled for 90 min. The cooled solution was neutralised with barium hydroxide (to pH 4) and barium carbonate, filtered, concentrated to 400 ml., and poured into ethanol (2 l.). The precipitated degraded polysaccharide A (*ca.* 50 g.) was separated, and the supernatant liquor was concentrated to 200 ml., passed through Amberlite resin IR-120(H) to remove barium ions and Amberlite resin IR-4B(OH) to remove acidic sugars, and concentrated to a syrup B(i) (*ca.* 35 g.). The degraded gum A (50 g.) in water (1 l.) was heated to 100°, 4N-sulphuric acid (140 ml.) was added, and the solution was boiled for 30 min. The hydrolysis products were worked up in the same way to give another syrupy mixture of sugars B(ii) (*ca.* 15 g.). The combined syrups B(i) and B(ii) (*ca.* 50 g.) in water (200 ml.) were adsorbed on charcoal–Celite (800 g.; 1 : 1). Elution with water afforded monosaccharides (36 g.) [arabinose, galactose, xylose, and rhamnose (trace)] and a small fraction (0·8 g.) in which

[12] Lewis and Smith, *J. Amer. Chem. Soc.*, 1957, **79**, 3929.

L-rhamnose was identified as the crystalline hydrate, m. p. 90—91° and mixed m. p. 89—90°, $[\alpha]_D$ −2·0° (5 min.) ⟶ +8·6° (1 hr., equil.) (*c* 1·63). Oligosaccharides were eluted with ethanol–water containing increasing proportions of ethanol. Ten fractions contained either pure oligosaccharides or mixtures from which pure compounds were isolated on refractionation. Other fractions which contained mixtures of oligosaccharides were not examined further.

Examination of Oligosaccharide-containing Fractions.—Fraction 1. Chromatography of the syrup (0·23 g.; eluted with water containing 2·5% of ethanol) showed 6-*O*-β-galactopyranosylgalactose, 3-*O*-β-arabopyranosylarabinose, and a pentose-containing disaccharide (R_{gal} 0·30, 0·83, and 0·67). Hydrolysis of the mixture gave galactose and arabinose. The two arabinose-containing disaccharides (R_{gal} 0·83 and 0·67) were chromatographically indistinguishable from the two reducing disaccharides formed by acid-catalysed reversion of L-arabinose.[10]

Fraction 2. The syrup (1·1 g.; eluted with water containing 2·5% of ethanol) contained a main component, R_{gal} 0·29 in solvent A, R_F 0·31 in solvent 3, together with traces of galactose, arabinose, and arabinose-containing disaccharides. The syrup (1·0 g.) was fractionated on cellulose (45 × 2 cm.) with solvent A to give fractions 2*a* (0·15 g.) and 2*b* (0·56 g.). Fraction 2*a* contained arabinose, galactose, and a mixture of arabinose-containing disaccharides in which 3-*O*-β-arabopyranosylarabinose predominated. Fraction 2*b*, $[\alpha]_D$ +31° (*c* 0·99 in water), was chromatographically pure and gave galactose only on hydrolysis. Methyl sulphate (1 ml.) and sodium hydroxide (1 ml.; 30%) were added dropwise during 1 hr. to the sugar (200 mg.) in water (5 ml.). Three more additions of methyl sulphate (12 ml.) and sodium hydroxide (17 ml.; 30%) were made, each during a period of 3 hr. and followed by stirring overnight. The reaction was completed by heating the solution on the boiling-water bath for 30 min., and the methylated sugar (202 mg.) was isolated by extraction with chloroform for 16 hr. Hydrolysis of the methylated disaccharide (150 mg.) with N-hydrochloric acid (7 ml.) at 100° for 4 hr., followed by neutralisation with silver carbonate yielded a mixture of sugars (140 mg.) which were separated into three fractions on cellulose (35 × 1·6 cm.) with light petroleum–butan-1-ol (7 : 3) saturated with water. Fraction (i) (40 mg.), $[\alpha]_D$ +105° (*c* 0·78 in water), R_G 0·90 in solvent B, was identified as 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose [aniline derivative, m. p. 198° and mixed m. p. (with sample of m. p. 189—190°) 190—192°]. Fraction (ii) (35 mg.) contained a mixture of tetra- and 2 : 3 : 4-tri-*O*-methylgalactose and a trace of a sugar (possibly 2 : 3 : 5-tri-*O*-methylgalactose), R_G 0·82 in solvent B. Fraction (iii) (39 mg.), $[\alpha]_D$ +106° (*c* 0·77 in water), R_G 0·70 in solvent B, was identified as 2 : 3 : 4-tri-*O*-methyl-D-galactose [aniline derivative, m. p. 159—160° and mixed m. p. (with sample of m. p. 164—165°) 161—162°].

Fraction 3. The syrup (205 mg.; eluted with water containing 5% of ethanol) contained a mixture of sugars and was fractionated on cellulose (45 × 2 cm.) with solvent A to give four fractions. Fraction 3*a* (65 mg.) contained arabinose, galactose, and three arabinose-containing disaccharides (R_{gal} 1·9, 1·33, and 1·22 in solvent A). Fraction 3*b* (10 mg.) contained 3-*O*-β-arabopyranosylarabinose (R_{gal} 0·83 in solvent A). Fraction 3*c* (30 mg.), $[\alpha]_D$ +125° (*c* 1·1 in water) and R_{gal} 0·35 in solvent A, contained a single component which gave galactose and glucose on hydrolysis. Hydrolysis of the derived glycitol gave only galactose. Fraction 3*d* (50 mg.) contained only 6-*O*-β-galactopyranosylgalactose.

Fraction 4. The sugar (155 mg.; eluted with water containing 5% of ethanol), after recrystallisation from ethanol–water, had m. p. 202—203°, $[\alpha]_D$ +80° (5 min.) ⟶ +62° (90 min., equil.) (*c* 0·77 in water), R_{gal} 0·60 in solvent A and R_F 0·38 in solvent C. Hydrolysis of the sugar gave galactose and arabinose, and of the derived glycitol only galactose. The sugar (100 mg.) was methylated as described above, giving the methylated disaccharide (100 mg.). Hydrolysis of this with N-hydrochloric acid at 100° for 3 hr. followed by neutralisation with silver carbonate, gave a syrup (85 mg.) which was separated into four fractions on cellulose (40 × 2 cm.) with light petroleum (b. p. 100—120°)–butan-1-ol (7 : 3) saturated with water. Fraction *a* (28 mg.), $[\alpha]_D$ +76° (*c* 0·52 in water), contained 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose (aniline derivative, m. p. and mixed m. p. 192—193°) and a trace of 2 : 5-di-*O*-methylarabinose. Fraction *b* (5 mg.), $[\alpha]_D$ *ca.* −20° (*c* 0·1 in water), R_G 0·85 in solvent B, was chromatographically indistinguishable from 2 : 5-di-*O*-methyl-L-arabinose. Fraction *c* (10 mg.) was a mixture of tri-*O*-methylgalactose (probably from incomplete methylation) and 2 : 4-di-*O*-methylarabinose. Fraction *d* (20 mg.), $[\alpha]_D$ +120° (*c* 0·3 in water), was chromatographically indistinguishable from 2 : 4-di-*O*-methyl-L-arabinose (R_G 0·60 in solvent B) and clearly distinct from the 2 : 3- and 3 : 4-dimethyl ethers in solvents B and D. An impure specimen of the

aniline derivative, m. p. 114—115° and mixed m. p. 114—117°, gave an *X*-ray powder photograph identical with that of the authentic specimen, m. p. 139—140°.

Fraction 5. The mixture of sugars (80 mg.) was separated on cellulose (45 × 2 cm.) with solvent A to give four fractions. Fraction 5*a* (25 mg.) contained a mixture of arabinose containing disaccharides (R_{gal} 1·18, 1·40, and 2·0). Fraction 5*b* (5 mg.) contained 3-*O*-β-galactopyranosylarabinose. Fraction 5*c* (25 mg.) crystallised from acetone–water, had m. p. 151—152°, $[\alpha]_D$ +69° ⟶ +55° (equil.) (*c* 1·4 in water), R_{gal} 0·35 in solvent A, and gave galactose only on hydrolysis. Oxidation of the disaccharide and of 3-*O*-β-D-galactopyranosyl-D-galactose with lead tetra-acetate followed by hydrolysis [9b] gave the same products including galactose and lyxose. The *X*-ray powder photograph of the sugar was identical with that of 3-*O*-β-D-galactopyranosyl-D-galactose. Fraction 5*d* (3 mg.) contained 6-*O*-β-galactopyranosylgalactose.

Fraction 6. The syrup (0·83 g.; eluted with water containing 7·5% of ethanol) contained a main component together with traces of 6-*O*-β-galactopyranosylgalactose and monosaccharides. A portion (0·58 g.) was separated on cellulose (45 × 2 cm.) with solvent A and a chromatographically pure sample (0·45 g.) of the oligosaccharide, $[\alpha]_D$ +20° (*c* 0·99 in water), R_F 0·20 in solvent C, was isolated. Hydrolysis of the sugar gave only galactose, and 6-*O*-β-galactopyranosylgalactose was the only disaccharide formed on partial hydrolysis. The sugar (200 mg.) was methylated as described previously to give the methylated trisaccharide (220 mg.), hydrolysis of which with N-sulphuric acid at 100° for 4 hr. afforded a mixture of methylated sugars which were separated on filter sheets with solvent B to give two fractions. Fraction (i) (36 mg.), $[\alpha]_D$ +100° (*c* 0·53 in water), contained 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose, R_G 0·90 (aniline derivative, m. p. and mixed m. p. 189—190°), and a trace of a second sugar, R_G 0·82 (possibly 2 : 3 : 5-tri-*O*-methylgalactose). Fraction (ii) (80 mg.), $[\alpha]_D$ +104° (*c* 0·77 in water), contained 2 : 3 : 4-tri-*O*-methyl-D-galactose, R_G 0·70 (aniline derivative, m. p. and mixed m. p. 159—160°), together with traces of the sugar with R_G 0·82.

Fraction 7. The sugar (265 mg.; eluted with water containing 7·5% of ethanol) after recrystallisation from ethanol–water had m. p. 191°, $[\alpha]_D$ +39° (equil.) (*c* 0·91 in water), R_{gal} 0·18 in solvent A, R_F 0·25 in solvent G. Partial acid hydrolysis of the trisaccharide afforded arabinose, galactose, 3-*O*-β-galactopyranosylarabinose, and 6-*O*-β-galactopyranosylgalactose, and of the derived glycitol only galactose and 6-*O*-β-galactopyranosylgalactose. The trisaccharide (200 mg.) was converted into its methylated derivative (202 mg.), hydrolysis of which with N-hydrochloric acid at 100° for 4 hr. gave a mixture of methylated sugars (180 mg.) which was separated into four fractions on cellulose (50 × 1·6 cm.) with light petroleum (b. p. 100—120°)–butan-1-ol (7 : 3), saturated with water. Fraction *a* (47 mg.), $[\alpha]_D$ +97° (*c* 2·1 in water), R_G 0·90 in solvent B, was 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose (aniline derivative, m. p. and mixed m. p. 190—191°). Fraction *b* (5 mg.), R_G 0·85 in solvent B, was identified as 2 : 5-di-*O*-methyl-L-arabinose by conversion into 2 : 5-di-*O*-methyl-L-arabonamide, m. p. and mixed m. p. 122°. Fraction *c* (40 mg.), R_G 0·70, was 2 : 3 : 4-tri-*O*-methyl-D-galactose [aniline derivative, m. p. 167—168° and mixed m. p. (with sample m. p. 164—165°) 164—165°]. Fraction *d* (32 mg.), $[\alpha]_D$ +107° (*c* 0·51 in water), R_G 0·60 in solvent B, was characterised by conversion into the aniline derivative of 2 : 4-di-*O*-methyl-L-arabinose, identified by m. p. and mixed m. p. 122° and by *X*-ray powder photograph.

Fraction 8. The chromatographically pure sugar (0·47 g.; eluted with water containing 10% of ethanol) had $[\alpha]_D$ +14° (*c* 1·95 in water), R_F 0·12 in solvent C. Hydrolysis gave only galactose, and 6-*O*-β-galactopyranosylgalactose was the only disaccharide detected on partial acid hydrolysis.

Fraction 9. The crystalline sugar (100 mg.; eluted with water containing 12·5% of ethanol), after recrystallisation from ethanol–water had m. p. 171°, $[\alpha]_D$ +26° (equil.) (*c* 0·90 in water), R_F 0·16 in solvent C. Hydrolysis of the tetrasaccharide gave galactose and arabinose in the proportion of 2·8 : 1. Arabinose, galactose, 3-*O*-β-galactopyranosylarabinose, and 6-*O*-β-galactopyranosylgalactose were formed on partial acid hydrolysis of the sugar, whereas similar treatment of the derived glycitol gave only galactose and 6-*O*-β-galactopyranosylgalactose.

Fraction 10. The sugar (115 mg.; eluted with water containing 15% of ethanol), after recrystallisation from ethanol–water, had m. p. 177—179° (decomp.), $[\alpha]_D$ +19° (equil.) (*c* 1·05 in water), R_F 0·10 in solvent C. Hydrolysis gave galactose and arabinose in the proportion of 3·7 : 1. Partial acid hydrolysis of the sugar gave arabinose, galactose, 3-*O*-β-galactopyranosylarabinose, and 6-*O*-β-galactopyranosylgalactose, and partial hydrolysis of the derived glycitol gave galactose and 6-*O*-β-galactopyranosylgalactose.

XUM

Experiments on Degraded Gum Ghatti.—A sample (158 mg.) of degraded gum ghatti [2] (uronic anhydride, 22%) was hydrolysed with 2N-sulphuric acid (5 ml.) at 100° for 24 hr. Ribose (23·3 mg.) was added to the cooled hydrolysate, and the mixture was neutralised with Amberlite resin IR-4B(OH), filtered, and concentrated. Samples (*ca.* 20 mg.) were separated on filter sheets with ethyl acetate–acetic acid–water (3 : 1 : 3; upper layer) and the quantities of mannose and ribose were determined by Flood, Hirst, and Jones's [13] method. The quantities of mannose corresponded to the presence of 6·3% of anhydromannose in the degraded gum (mean of three determinations). This is a minimum value since the hydrolysis conditions would not cause complete cleavage of aldobiouronic acids.

Bromine (0·5 ml.) was added to a solution of degraded gum (100 mg.) in water (100 ml.) over calcium carbonate (2 g.) and the mixture kept for 1 week at room temperature in the dark. Excess of bromine was removed by aeration, and the solution treated with silver carbonate, filtered, treated with hydrogen sulphide, again filtered, and concentrated. A second sample of degraded gum (100 mg.) was kept in oxygen-free saturated lime water (20 ml.) for 1 week at room temperature. The solution was neutralised with carbon dioxide, filtered, and concentrated to a syrup.

Samples (*ca.* 50 mg.) of degraded gum, degraded gum oxidised with bromine, and degraded gum treated with lime water were each hydrolysed with 0·5N-sulphuric acid at 100° for 30 min. The hydrolysates were absorbed on columns of charcoal–Celite (1 : 1; 25 × 1·8 cm.), monosaccharides were eluted with water (150 ml.), and water containing 20% of ethanol eluted mixtures of oligosaccharides.

Chromatography in solvent A showed that the degraded gum gave 3-*O*-β-galactosylarabinose and galactose-containing oligosaccharides as products of partial hydrolysis, but that the gums oxidised with bromine and treated with lime water gave galactose-containing oligosaccharides and only traces of 3-*O*-galactosylarabinose.

We thank the Rockefeller Foundation, the Distillers Company Limited, and Imperial Chemical Industries Limited for grants.

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF EDINBURGH. [*Received, July 10th,* 1958.]

[13] Flood, Hirst, and Jones, *J.*, 1948, 1679.

---

895. *Immunopolysaccharides. Part XI.* Structure of an* Acetobacter capsulatum *Dextran.*

By S. A. BARKER, E. J. BOURNE, G. T. BRUCE, and M. STACEY.

A polysaccharide elaborated by *Acetobacter capsulatum* is shown to be a branched dextran, in which the principal glucosidic linkages are α-1 : 6, and the branch points involve positions 1 and 4. The average change length is *ca.* 13 glucose residues.

PREVIOUS workers [1,2] had shown that the polyglucosan synthesised from a starch dextrin by *Acetobacter capsulatum* has serological properties very similar to those of a dextran synthesised from sucrose by a strain of *Leuconostoc mesenteroides*. The high yield of formic acid obtained [2,3] from periodate oxidation of the polysaccharides was indicative of the presence of 1 : 6-linked glucopyranose units. A batch of this polysaccharide, kindly provided by Dr. E. J. Hehre, has now been submitted to further investigation.

The polysaccharide, freed from amylaceous material by dialysis, was not stained by iodine under the standard conditions [4] used for the determination of the blue value of starch components. In agreement with Hehre [2] it was found that the polysaccharide was almost unattacked (*ca.* 1% conversion) by soya-bean β-amylase or salivary α-amylase.

* Part X, *J.*, 1958, 3468.

[1] Hehre and Hamilton, *Proc. Soc. Exp. Biol. Med.*, 1949, **71**, 336.
[2] Hehre, *J. Biol. Chem.*, 1951, **192**, 161.
[3] Hehre, personal communication, 1949.
[4] Bourne, Haworth, Macey, and Peat, *J.*, 1948, 924.

The hydrolysate of the polysaccharide was found to consist almost entirely of glucose (96% conversion), probably with a trace of fructose. The high optical rotation ($[\alpha]_D^{21}$ + 196°) and the infrared absorption spectrum [5] (max. at 837 cm.$^{-1}$ shown by α-anomers in the D-glucopyranose series) both indicated α-glycosidic linkages. Absorption peaks (914 and 766 cm.$^{-1}$) consistent with α-1 : 6-linkages were also present but no absorption at 794 cm.$^{-1}$ attributable to α-1 : 3-linkages was detected. Further evidence for α-1 : 6-linkages was obtained by the isolation of isomaltose, identified as its crystalline β-octa-acetate, from a partial hydrolysate of the polysaccharide. The main trisaccharide component of this partial hydrolysate was probably isomaltotriose since it gave only isomaltose and glucose when treated with N-sulphuric acid for 0·5 hr. at 90°.

Methylations of the dextran with sodium and methyl iodide in liquid ammonia [6] afforded a methyl ether having OMe, 42·7% (a tri-*O*-methylglucosan requires OMe, 45·6%) and ash, 3·1%. A paper chromatogram of a hydrolysate of the trimethyl ether revealed three components, having severally R_F values and staining properties identical with those of 2 : 3 : 4 : 6-tetra-, 2 : 3 : 4-tri-, and 2 : 3-di-*O*-methyl-D-glucose. Quantitative assay on filter paper, essentially as described by Hirst, Hough, and Jones,[7] showed that the percentage molecular proportion of each methyl sugar was: 2 : 3 : 4 : 6-, 7·6; 2 : 3 : 4-, 83·2; and 2 : 3-, 9·2. The *Acetobacter capsulatum* polysaccharide is thus shown to consist essentially of chains of α-1 : 6-D-glucopyranose units (average chain length *ca.* 13 glucose units) which are involved in branching through positions 1 and 4.

It is interesting that no evidence was found for the presence of 1 : 3-branches, which are now known to occur quite widely in dextrans. The low $[\alpha]_D$ value of the dextran in comparison with other dextrans confirms this.

Experimental

Purification of the Dextran.—The dextran (kindly supplied by Dr. E. J. Hehre) had been isolated by fractional precipitation with ethanol and methanol from culture media of *Acetobacter capsulatum* (NCTC 4943) utilising a soluble maize-starch dextrin as its carbon source. The dextran (1% w/w) was freed from traces of amylaceous material by dialysis for 5 days against repeated changes of distilled water and recovered by freeze-drying. After being dried *in vacuo* over phosphoric oxide at 60°, the dextran had ash, 0·2%; N, 0·3%; $[\alpha]_D^{21}$ +196° (*c* 0·18 in N-sodium hydroxide). Paper chromatography of the purified dextran, with butanol–ethanol–water–ammonia (40 : 10 : 49 : 1) as solvent and aniline hydrogen phthalate,[8] naphtharesorcinol,[9] and ammoniacal silver nitrate [10] as sprays failed to reveal any oligosaccharides. The dextran was not stained by iodine under standard [4] blue-value conditions.

Acidic Hydrolysis of the Purified Dextran.—The dextran (20 mg.) was hydrolysed with 1·4N-sulphuric acid (1 c.c.) at 100° for 5 hr. After removal of ions,[11] the neutral hydrolysate was examined by paper chromatography as above; the main component had an R_F value equal to that of glucose; traces of compounds which were probably fructose and hydroxymethylfurfuraldehyde were also detected. Determination [12] of the glucose produced when another sample of the dextran was hydrolysed for 5 hr. with 1·5N-sulphuric acid at 100° showed that the extent of the conversion was 96%.

Partial Acidic Hydrolysis of the Dextran.—The dextran (0·838 g.) was partially hydrolysed with N-sulphuric acid (37 c.c.) at 85° for 11 hr., $[\alpha]_D^{20}$ having then fallen to +131°. The acidic solution of saccharides was fractionated on a charcoal column [13] which was washed as shown in Table 1. Each eluate was neutralised with barium carbonate (when necessary), filtered, and concentrated to a syrup, and the saccharides were extracted with hot methanol or

[5] Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171.
[6] Freudenberg, Boppel, and Meyer-Delius, *Naturwiss.*, 1938, **26**, 123.
[7] Hirst, Hough, and Jones, *J.*, 1949, 928.
[8] Partridge, *Nature*, 1949, **164**, 443.
[9] *Idem*, *Biochem. J.*, 1948, **42**, 238.
[10] *Idem*, *Nature*, 1946, **158**, 270.
[11] Consden, Gordon, and Martin, *Biochem. J.*, 1947, **41**, 590.
[12] Bourne, Donnison, Haworth, and Peat, *J.*, 1948, 1687.
[13] Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677.

XUM

hot 50% aqueous methanol. Thereafter, they were obtained as freeze-dried powders and analysed by paper chromatography.

TABLE. 1. *Partial acidic hydrolysis of the dextran.*

Eluant	Fraction	Wt. (g.)	Probable sugar components
Water	A	0·252	Glucose, fructose (*ca.* 5%)
5% Ethanol (1)	B	0·129	Isomaltose
5% Ethanol (2)	C	0·102	Trisaccharide
10% Ethanol (1)	D	0·015	Trisaccharide, tetrasaccharide
10% Ethanol (2)	E	0·069	Tetrasaccharide
10% Ethanol (3)	F	0·030	Tetrasaccharide, pentasaccharide
10% Ethanol (4)	G	0·039	Pentasaccharide
35% Ethanol	H	0·176	Higher saccharides

Part (0·23 g.) of fraction A was characterised by conversion into penta-*O*-acetyl-β-D-glucopyranose (0·10 g.), m. p. and mixed m. p. 128—130°. Fraction B had $[\alpha]_D^{19}$ (uncorrected for ash) +111·1° (equil.) (*c* 0·41 in H_2O) (ash, 3·2%); Montgomery, Weakley, and Hilbert [14] report $[\alpha]_D^{25}$ +120° (equil.) (*c* 1·2 in H_2O), for isomaltose. A portion (0·048 g.) of fraction B, treated with acetic anhydride (0·5 c.c.) and fused sodium acetate (0·013 g.), gave β-isomaltose octa-acetate (0·036 g.), m. p. and mixed m. p. 144—146° (Found: C, 49·7; H, 5·8. Calc. for $C_{28}H_{38}O_{19}$: C, 49·6; H, 5·6%). Fraction C, after partial hydrolysis with N-sulphuric acid at 90° for 0·5, 1·0, and 2·0 hr., gave isomaltose and glucose (identified by paper chromatography).

Methylation of the Purified Dextran.—The dextran (1·1 g.) was treated with sodium and methyl iodide in liquid ammonia at −70° to −80° by a procedure similar to that of Freudenberg, Boppel, and Meyer-Delius.[6] After four additions of the methylating reagents (reaction times; sodium, 4—6 hr.; methyl iodide, 0·5 hr.) had been made, the ammonia was allowed to evaporate, with exclusion of moisture, the last traces being removed at 75°/20 mm. After dialysis the product (1·2 g.) was freeze-dried. This procedure was repeated thrice more, affording methyl ethers having OMe, 41·7%, 41·2%, and 38·8%, respectively. The final product was purified by Soxhlet-extraction with light petroleum (b. p. 60—80°) to remove grease and was then extracted with chloroform and dried. The methylated dextran (0·71 g.) showed OMe, 42·7% and ash, 3·1% (Calc. for $C_9H_{16}O_5$: OMe, 45·6%).

Identification of the Methyl Sugars obtained from the Methylated Dextran.—The polysaccharide ether (0·055 g.) in chloroform (1 c.c.) was treated with 8% (w/w) methanolic hydrogen chloride (1 c.c.) at 100° for 8 hr. and then, after removal of the solvent, with 4% hydrochloric acid (5·5 c.c.) at 100° for 6 hr. Paper-chromatographic analysis of the resulting methyl sugars revealed three components having R_F values and staining properties [8] identical with those of 2 : 3-di-*O*-methylglucose (R_G 0·69, brown stain), 2 : 3 : 4-tri-*O*-methylglucose (red stain), and 2 : 3 : 4 : 6-tetra-*O*-methylglucose and distinguishable from 2 : 4-di-*O*-methylglucose (R_G 0·64, red stain), 3 : 4-di-*O*-methylglucose (R_G 0·65, brown stain), and 2 : 3 : 6-tri-*O*-methylglucose (brown stain).

Determination of the Methyl Sugars obtained from the Methylated Dextran.—The remainder of the hydrolysate mentioned above was analysed by a method which was essentially that used by Hirst, Hough, and Jones [7] with minor modifications introduced by Barker, Bourne, and Wilkinson.[15] The results of three independent quantitative determinations based on oxidation with hypoiodite, are given in Table 2.

TABLE 2. *Quantitative analysis of the methyl sugars.*

	Molecular composition (%) indicated by assay no.			
Glucose derivative	I	II	III	Mean
2 : 3-Di-*O*-methyl	9·3	9·1	9·3	9·2
2 : 3 : 4-Tri-*O*-methyl	83·4	83·3	83·0	83·2
2 : 3 : 4 : 6-Tetra-*O*-methyl	7·4	7·6	7·7	7·6

We thank Dr. E. J. Hehre for the *Acetobacter capsulatum* polysaccharide. One of us (G. T. B.) thanks Courtaulds' Scientific and Educational Trust Fund for financial assistance.

CHEMISTRY DEPARTMENT, THE UNIVERSITY, BIRMINGHAM, 15.
CHEMISTRY DEPARTMENT, ROYAL HOLLOWAY COLLEGE,
ENGLEFIELD GREEN, SURREY.

[*Received, July 24th,* 1958.]

[14] Montgomery, Weakley, and Hilbert, *J. Amer. Chem. Soc.*, 1949, **71**, 1682.
[15] Barker, Bourne, and Wilkinson, *J.*, 1950, 3027.

XUM

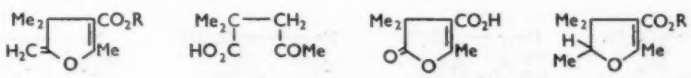
896. *The Reaction between 3-Chloro-3-methylbutyne and Methyl Sodioacetoacetate.*

By L. Crombie and K. Mackenzie.

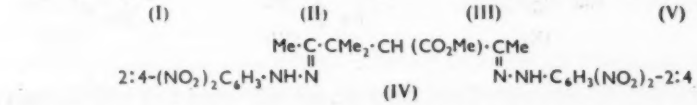
3-Chloro-3-methylbutyne and methyl sodioacetoacetate react according to the scheme on p. 4422. According to the conditions, various of six products are obtained, none of them containing a terminal acetylenic group. α-Reaction of the halide, followed by ring-closure, gives a 4 : 5-dihydro-5-methylene-3-furoic ester (I) (a novel type), and thence by action of acid other dihydrofuran derivatives (XXI, B and C). γ-Reaction, followed by deacetylation, leads to the methyl hexadienoate (XXIV), or if followed by Michael addition of more acetoacetate and cyclisation leads to the *cyclo*hexene derivative (XXVIII), which in light gives a dimer (a di*cyclo*hexano-*cyclo*butane). Structures of these products are established and some analogous reactions briefly studied.

According to the literature,[1] 3-chloropropyne yields the expected ethyl α-propynylacetoacetate when treated with ethyl sodioacetoacetate. We have found that if 3-chloro-3-methylbutyne is used in a similar reaction the distilled products give no colour with ferric chloride and show no terminal acetylenic absorption in the infrared spectrum. The nature of the products depends on the reaction conditions. When the halide (1·0 mol.) is treated with methanolic methyl sodioacetoacetate (1·1 mol.) for seven days at 20°, two products A and D are obtained. The same reaction under reflux conditions (20 hr.) gives product D, and a mixture of two compounds A and F which are separable by controlled hydrolysis but not by distillation. If, after reaction at the boiling point, much of the methanol is removed and the residue is poured into water and just acidified before completion of the working up, a fourth compound C intrudes and can be isolated by distillation. Varying the proportion of halide to sodioacetoacetate in the reflux reaction from 1 : 1·1 to 2 : 1 yields a new substance B, as well as D. All the products mentioned are liquid except D, and this, when exposed to light, forms another substance E. Apart from these substances, the low-boiling solvolysis and elimination products, 3-methoxy-3-methylbutyne and 2-methylbut-1-en-3-yne, could be formed but they are not considered further. These observations define the problem. In the sequel, first the constitutions of the six substances A—F are decided, and then the reaction is considered as a whole.

Substance A, $C_{10}H_{14}O_3$.—This is methyl 4 : 5-dihydro-2 : 4 : 4-trimethyl-5-methylene-3-furoate (I; R = Me), the first representative of the dihydromethylenefurans. The ester was slowly hydrolysed in a basic medium (sterically hindered and α-unsaturated methoxycarbonyl) to the crystalline acid (I; R = H) which re-formed the original ester when treated with diazomethane. On ozonolysis the ester yielded formaldehyde



(I) (II) (III) (V)



(IV)

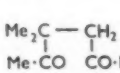
and, from the hydrolysed non-volatile fraction, dimethylmalonic acid. The acid (I; R = H) gave acetic acid and 2 : 2-dimethyl-4-oxopentanoic (mesitonic) acid (II) under similar degradative conditions: the enol-lactone (III) is the precursor of (II). These

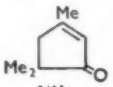
[1] Colonge and Gelin, *Compt. rend.*, 1953, **236**, 2074; **237**, 71, 393; *Bull. Soc. chim. France*, 1954, 208, 797; Gaudemar, *Ann. Chim.* (*France*), 1956, **1**, 161.

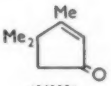
facts, taken with spectroscopic evidence and the formation of the bis-2 : 4-dinitrophenylhydrazone (IV) derived from a saturated diketone [max. 360 mμ (ε 43,500)] containing an ester function (1742 s cm.$^{-1}$), clearly demonstrate the structure (I; R = Me) for substance A.

In the ultraviolet spectrum the ester (I; R = Me) had a maximum at 266 mμ (ε 14,300) which was not shifted by alkali, whilst in the infrared range there were bands at 1695 s (α-unsaturated ester; frequency lower than usual), 1656 m and 889 m ($H_2C{:}C{\cdot}O^-$) and 1637 m cm.$^{-1}$ (conjugated $C{:}C{\cdot}CO^-$). On hydrogenation over palladium one mol. of hydrogen was slowly absorbed and the product [ultraviolet max. 256 mμ (ε 10,100)] contained only two of the four infrared bands mentioned, those due to the vinyl group having disappeared. This ester (V; R = Me) could be hydrolysed to the same crystalline acid (V; R = H) as was obtained when the unsaturated acid (I; R = H) was similarly hydrogenated.

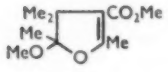
Further evidence for the correctness of structure (I) came from acidic hydrolysis of the acid (I; R = H). This gave 3 : 3-dimethylhexane-2 : 5-dione (VI) which was converted into 2 : 2-dimethylsuccinic acid by the haloform reaction and cyclised to a mixture of the trimethyl*cyclo*pentenones (VII) and (VIII) [2] in the presence of base. The *cyclo*pentenone mixture had the expected spectroscopic properties, formed a red α-unsaturated 2 : 4-dinitrophenylhydrazone, and on oxidation yielded mesitonic acid which must come from the isomer (VII).

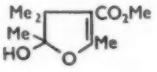

(VI)

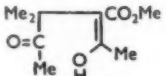

(VII)

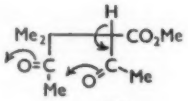

(VIII)

Substances B, $C_{11}H_{18}O_4$, *and C*, $C_{10}H_{16}O_4$.—The empirical formulæ for B and C differ from that of the ester (I; R = Me) by the elements of methanol and water respectively, and their kinship to this structure is seen from the fact that all three substances give the same bis-2 : 4-dinitrophenylhydrazone (IV) in acid solution. From this, and the ultraviolet [max. 250 mμ (ε 10,900); insignificantly affected by alkali] and infrared [1695 s (α-unsaturated ester) and 1639 s (conjugated $C{:}C{\cdot}O^-$), no vinylic ether absorption near 1656 cm.$^{-1}$] spectra, substance B must be methyl 4 : 5-dihydro-5-methoxy-2 : 4 : 4 : 5-tetramethyl-3-furoate (IX). In confirmation it can be prepared in excellent yield from the vinyl ether (I; R = Me) by treating the latter at 20° with methanol containing a drop of sulphuric acid. Structure (X) might therefore be expected for substance C and two further chemical facts are in agreement: first, the "glycosidic" hydroxyl group is methylated by acidic methanol to give substance B (IX), and secondly, the substance C is easily prepared by shaking the vinyl ether (I; R = Me) with dilute aqueous acid at room temperature.


(IX)


(X)


(XI)


(XII)

The spectral results for substance C are, however, not fully consistent with formula (X). In the ultraviolet region (ethanol) there is a maximum in the expected position (252 mμ) but the molecular extinction coefficient is only 2200 (in alkaline solution this band slowly declines in intensity and a new one arises at 280 mμ). Similarly, a liquid-film infrared spectrum shows the expected hydroxylic band at 3440 cm.$^{-1}$ (broad) but the carbonyl

[2] Sargent, *J. Org. Chem.*, 1942, **7**, 154; Wallach, *Annalen*, 1915, **408**, 202; 1924, **437**, 190.

double-bond region is complex with bands at 1743 s (α-saturated CO_2Me), 1724 shoulder (saturated C:O), 1710 s (α-unsaturated CO_2Me) and 1634 m cm.$^{-1}$ (conjugated C:C·O⁻). These conflicting data are reconciled if it is accepted that compound (X) is but one component of a tautomeric mixture. Two other species (XI) and (XII) must be taken into account. Compound (XII) is certainly present, but the extent to which (XI) participates in the equilibrium is less certain. The substance C gives no colour with alcoholic ferric chloride even when kept with the reagent for a week. It is true that compound (XI) is a *trans*-enol and that such substances do not give an immediate ferric chloride colour, but often colour gradually develops because of stereomutation to the iron salt of the *cis*-enol which forms a coloured stable chelate.*[3] This suggests that the concentration of form (XI) may be small and that the main equilibrium is between (X) and (XII), the proton on $C_{(3)}$ ionising and returning to the oxygen at $C_{(5)}$ as shown. As such it is a linked triad and ring-chain tautomeric system, pentad overall. If we discount formula (XI), infrared analysis using the ·C=C· stretching vibration for (X) (1633 cm.$^{-1}$ in chloroform) shows that substance C in approx. 0·7% solution in chloroform contains 19·7—22·3% of (X) depending on whether compound (V) or (IX) is used as the intensity standard. Similarly, analysis by ultraviolet methods gives a content of 21·0—19·5% in chloroform (c ~0·04%) and 21·6—20·1% in ethanol depending on whether (V) or (IX) is the standard.

Nuclear magnetic resonance data (see Table) are also only reasonably interpreted by considering material C to be a tautomeric mixture. No evidence in favour of the species (XI) was obtained however, inasmuch as no band due to a bonded enolic proton could be detected in the 700—1000 toluene unit region (methyl acetoacetate and ethyl α-methylacetoacetate have bands at 797 and 765 respectively): the lower limit of detection was 1%. The band for methyl protons in the environment HO·C(CH_3)·O in structure (X) lies on the side of that due to the ·C(CH_3)$_2$ band in the tautomeric mixture C. Estimation of relative areas gives a rough figure of 21% for the concentration of compound (X) in the neat liquid. Rough estimates for (X) based on the band areas of peaks assigned to ·O·C(CH_3)=C· and CH_3·CO· give 25% and 33% when the *gem*-dimethyl standard is used.

Nuclear magnetic resonance: chemical shifts.

(I)	>C(CH_3)$_2$ 1215; ·CO_2CH_3 1125; ·O·C(CH_3):C 1181; H_2C: 1096 (a pair of doublets).
(V)	>C(CH_3)$_2$ 1217 (doublet 7 c.p.s.); CO_2CH_3 1121; O·C(CH_3):C 1181; CH_2·CH·O 1216 (doublet 6 c.p.s.); CH_3·CH·O 1097 (quartet 6 c.p.s.).
(IX)	>C(CH_3)$_2$ 1218 (doublet 4 c.p.s.); CO_2CH_3 1118; O·C(CH_3):C (side-band) 1180; CH_3·C(O·)·OCH_3 1209; CH_3·C(O·)·OCH_3 1134.
(X) ⇌ (XII)	>C(CH_3)$_2$ 1218 (doublet 5 c.p.s.); CO_2CH_3 1118; O·C(CH_3):C and CH_3·CO 1183; CH_3·C(O·)·OH 1209 (infl.).
Me·CO·CH_2·CO_2Me ⇌ Me·C(OH):CH·CO_2Me	:C(CH_3)·OH 797; CH_3·CO 1185; CO_2CH_3 1127; CO·CH_2·CO_2CH_3 1132.
Me·CO·CHMe·CO_2Et ⇌ Me·C(OH):CMe·CO_2Et	:C(CH_3)·OH 765; CH_3·CO 1185; CO_2·CH_2·CH_3 1106 (quartet); CO_2·CH_2·CH_3 1223 (triplet); CO·CH(CH_3)·CO_2Et 1129 (quartet); CH_3·CH(CO·CH_3)·CO_2Et 1223 (doublet).
Me·CO·Et	CH_3·CO 1195; CH_3·CH_3 1187 (doublet; partially resolved); CH_3·CH_3 1241 (triplet).
Me·CO·CMe_2·CH_2·CO·Me	CH_3·CO 1187; Me·CO·C(CH_3)$_2$ 1224; Me·CO·CH_3 1155.

* Measured on pure liquids relative to water at 21° and expressed in toluene units (aromatic hydrogen 1000 units by definition).

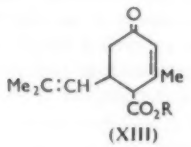
During these determinations, some chemical shifts for the dihydromethylenefuran (I), its dihydro-derivative (V), and the methoxy-compound (IX) were measured and agree with the proposed structures (Table above). Two points relating to splitting are relevant. First, in compounds (V) and (IX), and in mixture C, the *gem*-dimethyl bands are

* This is so for 3-*iso*propylacetylacetone (14% enol) but α-*iso*propylacetoacetic ester (1% enol) gives no colour even on storage.

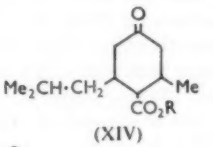
[3] Henecka, (*a*) "Chemie der Beta-dicarbonyl Verbindungen," Springer-Verlag, Berlin, 1950, p. 122; (*b*) *Chem. Ber.*, 1948, **81**, 189.

split through chemical shift as each methyl lies in a different environment. In (I) the environments are identical and the *gem*-dimethyl band is single. Secondly, the $H_2C=$ band is split as a pair of doublets in (I) because the environments of the two protons, this time within the plane of the ring, are not identical.

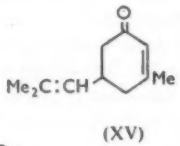
Substance D, $C_{13}H_{18}O_3$.—This substance proved to be methyl 6-*iso*but-1′-enyl-2-methyl-4-oxo*cyclo*hex-2-enecarboxylate (XIII; R = Me). It had an ultraviolet maximum at 232 mμ (ε 13,000) and infrared bands at 1733 s (ester), 1661 s (α-unsaturated ketone), 1623 m (conjugated ·C:C·) and 851 m cm.$^{-1}$ (RR′C:CH). The α-unsaturated keto-function was further demonstrated by spectroscopic data for the semicarbazone and the red 2 : 4-dinitrophenylhydrazone. Ozonolysis gave an excellent yield of acetone. Though the substance gave no colour with ferric chloride, it was hydrolysed, under carefully defined basic conditions, to the crystalline acid (XIII; R = H) which re-formed the original ester (XIII; R = Me) when treated with diazomethane but was decarboxylated at its melting point. On the other hand, the saturated compound (XIV; R = Me), formed by hydrogenating the ester (XIII; R = Me) over palladium in ethyl acetate, gave on hydrolysis an acid (XIV; R = H) which was not decarboxylated when heated above the melting point. These facts establish the vinylogous β-keto-ester group as in formula (XIII).



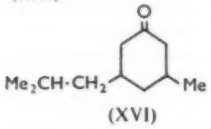
(XIII)



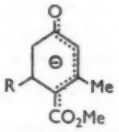
(XIV)



(XV)



(XVI)



(XVII)

If basic hydrolysis of the ester (XIII; R = Me) was prolonged, decarboxylation ensued to give the ketone (XV) having an ultraviolet maximum at 230 mμ (ε 13,000) and infrared bands at 1672 s (α-unsaturated ketone) and 1631 m (conjugated ·C:C·); the 2 : 4-dinitrophenylhydrazone had the expected light-absorption. The same ketone, contaminated with an α-saturated isomer (ketone band 1718 cm.$^{-1}$) was obtained after the thermal decarboxylation mentioned above and indicates the operation of the well-known cyclic transition-state mechanism which results in a βγ-shift. By hydrogenating the ketone (XV), the saturated ketone (XVI) was prepared; its 2 : 4-dinitrophenylhydrazone proved to be the same as a synthetic specimen prepared from the hydrogenation product of authentic 5-*iso*butyl-3-methyl*cyclo*hexenone. This establishes the relationship of the *iso*butenyl, methyl, and oxo-groups in the compound (XIII) and completes the proof of structure. The open methylene position alpha to the keto-group is also demonstrated by the formation of a dibenzylidene derivative by the dimer E (below).

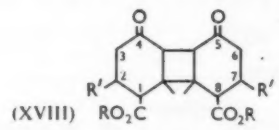
Another observation supporting structure (XIII) is the shift of maximal absorption in ~0·01N-alkali to 394 mμ (ε 9000): methyl 2-methyl-4-oxo*cyclo*hex-2-enecarboxylate (Hagemann's ester) shows a parallel shift from 232 mμ (ε 11,800) to 390 mμ (ε 9500). Presumably this is due to formation of the ambidentate ion (XVII; R = Me_2C:CH· or H). It is well known in this context that the anion of Hagemann's ester is alkylated in the 3-position.[4]

Substance E, $C_{26}H_{36}O_6$.—The *cyclo*hexenone (XIII; R = Me) forms large diamond-shaped crystals which when kept in light become opaque through formation of a dimer.

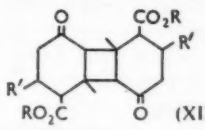
[4] Edgar, Harper, and Kazi, *J.*, 1957, 1083.

The latter is readily isolated since it is sparingly soluble in methanol. This dimerisation is more conveniently carried out (>80% yield) by exposing finely ground material to light from an ultraviolet lamp. Work on this photodimer is not yet complete and it is not directly involved in the reaction to be discussed below. Nevertheless its di*cyclo*hexano*cyclo*butane structure is certain and this supports the structure for compound (XII) since other 3-methyl*cyclo*hex-2-enones are known to dimerise in ultraviolet light (though in solution in methanol–water).[5] Apart from stereochemical features, the outstanding point to be decided is whether it has a parallel (XVIII) or antiparallel (XIX) structure: this must be governed by the crystal lattice of compound (XIII). Subsequent discussion will be in terms of structure (XIX) but without prejudice to the alternative.

The ebullioscopic molecular weight agreed exactly with the dimer structure (XIX; R = Me, R′ = $CH{:}CMe_2$) and there was no high-intensity ultraviolet absorption. The yellow-orange bis-2 : 4-dinitrophenylhydrazone showed that the keto-function was unconjugated in the usual sense [max. 368 mμ (ε 47,500)]. In the infrared spectrum there were bands at 1739 s (saturated ester), 1695 s (saturated keto alpha to *cyclo*butane) and 850 m cm.$^{-1}$ ($Me_2C{:}CH\cdot$), and the two reactive methylenic positions were demonstrated by formation of a dibenzylidene derivative. On hydrogenation a tetrahydro-derivative (XIX; R = Me, R′ = $Me_2CH\cdot CH_2$) was formed, whilst ozonolysis of the dimer gave



(XVIII)



(XIX)

>1 mol. of acetone and the diacid diester (XIX; R = Me, R′ = CO_2H). The resistance of the parent dimer to hydrolysis corroborates the hindered position of the ester function. Thus, of the functional groupings in (XIII), only the α-double bond has disappeared, and this without formation of a new double bond between two molecules of monomer. Only the di*cyclo*hexano*cyclo*butane system is therefore acceptable.

Substance F, $C_8H_{12}O_2$.—Though efficiently fractionated, this substance could not be adequately separated from the dihydromethylenefuran (I). Since the latter is hydrolysed slowly, the mixture was stirred with 5% aqueous sodium hydroxide and the acid derived from compound F was isolated almost quantitatively. It was re-esterified with diazomethane to give pure compound F. Infrared analysis showed that the mixture used contained 25·4% of compound F and 74·6% of compound (I), and a synthetic mixture of these proportions exactly simulated the infrared curve of the original. Chemical analysis, performed by adding methanol to component (I) under acid conditions and then estimating the content of compound F in the mixture by hydrogenation, showed 26·3% of compound F.

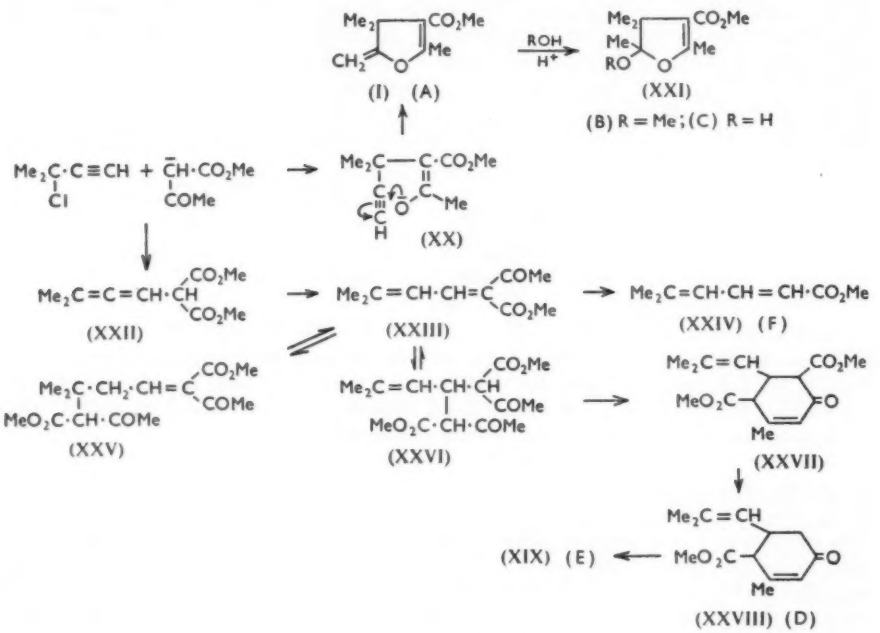
Compound F was shown to be methyl 5-methylhexa-2 : 4-dienoate as follows. The crystalline acid, m. p. 113°, had a maximum at 272 mμ (ε 24,000) and formed a crystalline *p*-bromophenacyl ester. There were infrared bands at 1681 s (α-unsaturated CO_2H), 1626 s and 1600 s (conjugated diene), and 995 m cm.$^{-1}$ (conjugated *trans*-$CH{:}CH\cdot$). On hydrogenation two mols. of hydrogen were absorbed and the product, 5-methylhexanoic acid, was identified by comparing its *p*-bromophenacyl ester with an authentic specimen. As the only literature reference [6] to 5-methylsorbic acid gave m. p. 105°, the identification was made rigorous by preparing the acid in another way, by a Reformatski reaction between 3-methylcrotonaldehyde and ethyl bromoacetate, and comparing the *p*-bromophenacyl esters of the two specimens.

We are now in a position to consider the main reaction.

The Reaction between 3-*Chloro*-3-*methylbutyne and Methyl Sodioacetoacetate.*—The

[5] Triebs, *Ber.*, 1930, **63**, 2738; *J. prakt. Chem.*, 1933, **138**, 299.
[6] Reid and Sause, *J.*, 1954, 516.

products A—F are accommodated by the annexed scheme involving net α- and γ-attack on the acetylenic halide.* At this stage no examination of the detail of the phase which initiates the reaction has been made, but a parallel with corresponding reactions of allylic halides is obvious. In view of the nucleophilic character of the reagent, the fairly low ionising power of the solvent ($Y = -1{\cdot}09$),[9] and the fact that the S_N1 solvolysis of 3-chloro-3-methylbutyne in 80% ethanol is very much slower than the S_N2 hydrolysis,[10] the reaction will be considered, for the present, as an S_N2 and S_N2' replacement. The considerable S_N2' element in the reaction is then ascribed to steric screening of $C_{(3)}$ by the *gem*-dimethyl grouping and the unhindered character of $C_{(1)}$. It is to be noted, however, that formation of a 3-methylbutynyl enol ether of acetoacetic ester by *O*-alkylation, followed by a cyclic rearrangement, could also provide an explanation for the γ-attack.



Direct α-attack must lead initially to methyl 2-(1 : 1-dimethylpropynyl)acetoacetate, the enolate (XX) of which cyclises as shown to yield compound A. If the reaction is conducted with halide in considerable excess the pH change in the solution, when all the base has been consumed, enables addition of methanol to the dihydromethylenefuran to proceed and compound B is formed. This was confirmed by refluxing together methanol, 3-chloro-3-methylbutyne, and the dihydromethylenefuran (I), which gave an excellent

* In this connexion Zakharova reports [7] that 3-chloro-3-methylbutyne, when treated with silver acetate in glacial acetic acid, gives 1-acetoxy-3-methylbuta-1 : 2-diene and 1 : 2-diacetoxy-3-methylbut-2-ene as well as 3-acetoxy-3-methylbutyne. Pudovic [8] also reports γ-attack by triethyl phosphite on this halide.

[7] Zakharova, *Zhur. obshchei Khim.*, 1945, **15**, 425; 1947, **17**, 686, 1277; 1949, **19**, 1297; *J. Gen. Chem.* (*U.S.S.R.*), 1949, **19**, 75; Zakharova and Dobromyslova, *ibid.*, 1950, **20**, 2099; Zakharova and Sapozhnikova, *ibid.*, 1952, **22**, 1843.

[8] Pudovic, *ibid.*, 1950, **20**, 97; 1951, **21**, 1593.

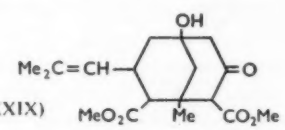
[9] Eliel in Newman's "Steric Effects in Organic Chemistry," Wiley, New York, 1956, p. 69.

[10] Burawoy and Spinner, *J.*, 1954, 3752; Hennion and Maloney, *J. Amer. Chem. Soc.*, 1951, **73**, 4735; Hennion and Nelson, *ibid.*, 1957, **79**, 2142.

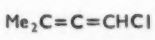
yield of compound B. The origin of small amounts of compound C if aqueous suspensions of the precursor A are acidified during the working up is obvious.

The γ-attack must involve the initial formation of an allenic acetoacetate (XXII) which would be expected to rearrange prototropically [11] in a fast reaction to give the diene (XXIII). Depending on the conditions, the latter can be deacylated to yield the diene ester F, or undergo a Michael reaction with more acetoacetate.* Michael addition, which has long been recognised as reversible, could occur 1 : 2 or 3 : 4 (or 1 : 4 if prototropic equilibrium is not established). Since irreversible cyclisation of the product from the 1 : 2 mode of addition occurs readily in basic media, only this is of significance here. The product (XXVII) undergoes hydrolysis and decarboxylation in the presence of base (the preparation of Hagemann's ester is a well-known analogy) to yield the crystalline *cyclo*hexenone D.

In the reaction at reflux temperature between 3-chloro-3-methylbutyne (1·0 mol.) and methyl sodioacetoacetate (1·1 mol.), the isolated yield of diene ester F was 9·5% and of the *cyclo*hexenone D, 3%. At 20°, however, the deacylation is less able to compete with formation of compound D, and the yield of this rises to 8%, whilst the hexadienoate F is not found. Similarly, and in agreement with the proposed scheme, the use of two mol. of acetoacetate to one of halide causes the yield of compound D to rise to 9% and the diene F could not be detected: the yield of methylenefuran A was 72%. Although accumulation of compound D at the expense of F, since both are derived from the common intermediate (XXIII), seems logical, it is to be noted that, particularly when excess of acetoacetic ester is employed, the disappearance of the diene ester F may also be associated with its involvement in a Michael addition. The reaction is too complex for more than a qualitative assessment of the importance of competing reaction paths since the crystalline *cyclo*hexenone is always isolated from high-boiling fractions containing uncrystallisable yellow viscous oils which are very difficult to purify. Some show hydroxylic infrared absorption and give colours with ferric chloride. According to circumstances, dehydroacetic acid, Michael addition products, and other substances might be present but we know little of the amounts involved. In particular we have searched for the product of a Rabe reaction [13] from compound D, the bicyclic ketone (XXIX), but it has not been found.



(XXIX)



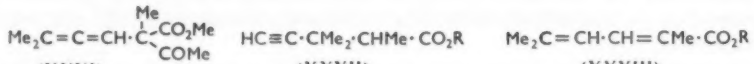
(XXX)

Two other points in connexion with the part of the reaction involving γ-attack have received some attention. First, there is the possibility that part of the 3-chloro-3-methylbutyne isomerises to 1-chloro-3-methylbuta-1 : 2-diene [14] (XXX) before reaction and that this then undergoes a normal displacement reaction. In experiments at 20° this can be ruled out, for it was found that the chloroallene and methyl sodioacetoacetate in methanol underwent no appreciable reaction in seven days and only unchanged reagents could be isolated. Under reflux conditions (16 hr.) about 5% of an impure product containing the dihydromethylenefuran A and the diene F in the ratio 2·2 : 1 was isolated. One possible explanation is that the allenic halide (XXX) is undergoing slow reaction by an S_N2' and an S_N2 path.

* Michael addition to 6-methylhepta-3 : 5-dien-2-one is not a suitable alternative as the product of 1 : 2-addition would be expected, from analogies,[12] to give methyl 6-*iso*but-1′-enyl-4-methyl-2-oxo*cyclo*hex-3-enecarboxylate.

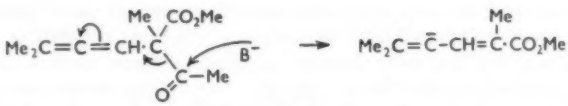
[11] Jones, Witham, and Whiting, *J.*, 1954, 3201.
[12] See ref. 3(*a*), p. 263.
[13] Rabe and Appuhn, *Ber.*, 1943, **76**, 982, who refer to the earlier work.
[14] Hennion, Sheehan, and Maloney, *J. Amer. Chem. Soc.*, 1950, **72**, 3542.

Secondly, if methyl sodio-α-methylacetoacetate is used in the reaction with 3-chloro-3-methylbutyne it might be possible to isolate the allene (XXXI) which could not undergo the usual prototropic rearrangement. Under reflux conditions (20 hr.) a mixture of esters, showing no appreciable infrared allenic absorption, was isolated. After hydrolysis, the two acids expected from α- and γ-attack were isolated crystalline. The first (XXXII; R = H) had infrared bands at 3236 s, 2112 mw (·C≡CH), and 1724 s (saturated CO_2H) and absorbed two mol. of hydrogen on catalytic hydrogenation: its precursor methyl α-(1 : 1-dimethylpropynyl)-α-methylacetoacetate, cannot cyclise to a dihydromethylenefuran as no enolic hydrogen is available. The other (XXXIII; R = H) was identified

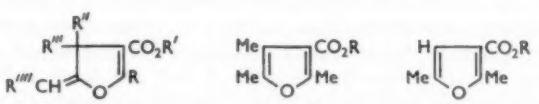


(XXXI) (XXXII) (XXXIII)

by spectroscopic data and direct comparison with authentic 2 : 5-dimethylhexa-2 : 4-dienoic acid.[15] In attempts to trap the allene (XXXI) the reflux period was reduced to 30 min. and finally the reaction was carried out at 20° for 90 min. In both cases ultraviolet data indicated that appreciable amounts of the diene (XXXIII; R = Me) had been formed but infrared analysis showed that only very small quantities of allene were present: in some experiments it was not detectable. The allene must be removed by a fast reaction which does not involve the prototropic shift available for the methyl acetoacetate case. The simplest explanation seems to be a rapid deacylation-isomerisation mechanism:



Comment on the scope of the reaction between substituted α-acetylenic halides and β-keto-esters as a method for making dihydromethylenefurans can only be made in a most superficial manner but may provide indications for further work. By varying the structure of the reactants, the alkyl groups R, R′, R″ and R‴ in (XXXIV) can be varied, but a case in which R⁗ is other than H has not been tested. If R‴ is H (*e.g.*, employing 3-chlorobutyne in the reaction), the product from a reaction under reflux conditions contains both dihydromethylenefuran and furan ester (XXXV; R = Et), as demonstrated by ozonolysis and spectroscopic study of the fractions. On hydrolysis, only the crystalline furoic acid (XXXV; R = H), formed by prototropic rearrangement and identical with authentic 2 : 4 : 5-trimethyl-3-furoic acid,[16] was obtained. In the case of 3-chloropropyne (R‴ = R″ = H), the product is complex and, even though refluxing is prolonged, successive fractions from the distillation contain much terminally acetylenic material. Spectroscopic results and ozonolysis show that both the dihydromethylenefuran and



(XXXIV) (XXXV) (XXXVI)

furoic ester (XXXVI; R = Et) are present and hydrolysis gave the furoic acid (XXXVI; R = H), identical with authentic material.[17] Base-catalysed cyclisation in this case seems to be much less favoured than when R″ = R‴ = Me. Colonge and Gelin [1] have

[15] Crombie, Harper, and Sleep, *J.*, 1957, 2743.
[16] Reichstein, Zschokke, and Syz, *Helv. Chim. Acta*, 1932, **15**, 1112.
[17] Dann, Distler, and Merkel, *Chem. Ber.*, 1952, **85**, 457.

observed that ethyl α-propargylacetoacetate gives 2 : 5-dimethyl-3-furoic acid if refluxed for 4 hours with 50% sodium hydroxide solution and suggest a preliminary acetylene–allene rearrangement. The above results indicate that this postulate is unnecessary and that internal addition involves the terminal acetylenic linkage: prototropic rearrangement then follows.

Experimental

The ultraviolet absorptions (Mrs. A. I. Boston) were determined for solutions in pure ethanol (unless another solvent is indicated) using either a Spectracord recording instrument or a Unicam S.P. 500 manual instrument. Infrared measurements (Mr. R. L. Erskine) were made with a Grubb-Parsons double-beam instrument; unless stated otherwise, liquid samples were examined as pure films, and solid samples as paraffin mulls. Nuclear magnetic resonance data were obtained with a Varian (40 mc) instrument.

Reaction between Methyl Sodioacetoacetate and 3-*Chloro*-3-*methylbutyne at* 20°.—The chloro-compound was prepared by a known method [14] and purified by fractionation through a column packed with glass helices (b. p. 75°, n_D^{21} 1·4180): all samples were examined spectroscopically to ascertain freedom from allenic and other impurities. 3-Chloro-3-methylbutyne (46·1 g., 0·45 mol.) was added dropwise to methyl sodioacetoacetate (at 20°) prepared from sodium (11·5 g.), methyl acetoacetate (58 g., 0·5 mol.), and dry methanol (250 ml.). The mixture was set aside: sodium chloride began to be deposited after 12 hr. After 7 days the mixture was filtered and the filtrate evaporated. The pale yellow liquid, after being held *in vacuo*, showed no acetylenic absorption in the infrared region: it was poured into water and extracted with ether. The ethereal layer was dried (Na_2SO_4), evaporated, and distilled to give a fraction b. p. 85—108°/20 mm. (42·8 g.). This was contaminated with a little methyl acetoacetate but on redistillation *methyl* 4 : 5-*dihydro*-2 : 4 : 4-*trimethyl*-5-*methylene*-3-*furoate* (I) was obtained pure, b. p. 98°/20 mm., $n_D^{21\cdot5}$ 1·4803—1·4810, giving no ferric chloride reaction (Found: C, 66·05; H, 7·95. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%). In ~0·01N-ethanolic alkali, the absorption max. remained at 266 mμ (ε after 0, 4, and 24 hr.; 16,400, 16,300, and 12,200).

Continuing the main distillation at 0·1 mm. gave, after rejection of a small intermediate cut, a fraction of b. p. 120—145° (15·5 g.) which solidified with evolution of heat. When stirred with a little cold methanol and filtered, the solid gave *methyl* 6-iso*but*-1′-*enyl*-2-*methyl*-4-*oxocyclohex*-2-*enecarboxylate* (XIII) (8 g.): crystallisation from methanol gave large colourless diamond-shaped crystals, m. p. 73° [Found: C, 70·3; H, 8·2%; *M* (Rast), 222·4. $C_{13}H_{18}O_3$ requires C, 70·25; H, 8·15%; *M*, 222·3].

Reaction between Methyl Sodioacetoacetate and 3-*Chloro*-3-*methylbutyne in Refluxing Methanol.*—3-Chloro-3-methylbutyne (238 g., 2·32 moles) was added dropwise to a stirred and refluxing solution of methyl sodioacetoacetate prepared from sodium (58·7 g., 2·55 g.-atoms), methyl acetoacetate (296 g., 2·55 moles), and dry methanol (1·2 l.). Heating and stirring were continued (20 hr.). After filtration, most of the methanol was removed by distillation and the product was poured into water, neutralised, and extracted with ether. After drying and evaporation, the extract was distilled through a 2 ft. 6 in. Stedman gauze-packed column with a variable take-off head. Twenty-one fractions of approximately equal size were taken with the b. p. approximately constant (90°/~10 mm., pressure controlled by an electrically operated manostat), except for the first fraction (b. p. 84—88°/11 mm., n_D^{20} 1·4898). The contents of tubes 2 and 3 had n_D^{20} 1·4926 and n_D^{20} 1·4931: the refractive index then fell steadily (tube 5, n_D^{20} 1·4924; tube 9, n_D^{20} 1·4919; tube 17, n_D^{20} 1·4884; tube 21, n_D^{20} 1·4819) (Found, for fraction 5: C, 66·1; H, 8·15. Found, for fraction 17: C, 66·5; H, 8·2. Calc. for $C_8H_{12}O_2$: C, 68·55; H, 8·65. Calc. for $C_{10}H_{14}O_3$: C, 65·9; H, 7·75%). Infrared spectra of the contents of tubes 1, 5, 17, and 21 showed that the products were mixtures of methyl 5-methylsorbate and methyl 4 : 5-dihydro-2 : 4 : 4-trimethyl-5-methylene-3-furoate, the concentration of the former decreasing in the later fractions. Fractions 1—21 were united (mixture M, 120 g.), n_D^{21} 1·4896. The ultraviolet max. was at 270 mμ ($E_{1\,cm.}^{1\%}$ 900). The composition of this mixture was estimated by an infrared method using intensity measurements (CS_2) for bands at 877 cm.$^{-1}$ (methyl 5-methylsorbate) and 889 cm.$^{-1}$ (furan ester). It contained 25·4% of the sorbate and 74·6% of the furan: a synthetic mixture of this composition, n_D^{21} 1·4899, gave an infrared spectrum (liquid film) identical with that of the united fractions 1—21 (M).

XUM

The composition was also estimated by adding the mixture (0·51 g.) to methanol (10 ml.) containing a drop of sulphuric acid and after 4 hr. neutralising it with methanolic potassium hydroxide and hydrogenating the resultant mixture of methyl sorbate and the methoxy-compound (IX) over 5% palladium–barium sulphate. The uptake was 46 ml. of hydrogen (20°/760 mm.) corresponding to 26·3% of diene-ester.

Distillation was continued: fractions 22, 23, and 24 had respectively n_D^{20} 1·4786 (5·9 g.), n_D^{20} 1·4654 (4·8 g.), and n_D^{20} 1·4866 (2·0 g.). The next group of fractions (25—30) had b. p. 148°/15 mm., n_D^{20} 1·4866—1·5042 (29·3 g.), and partially crystallised. Finally, with the distillation temperature unsteady, a yellow oil (11·5 g.) (which did not crystallise, even when seeded) was obtained. The contents of tubes 24—29 were triturated with methanol at 0° and methyl 6-*iso*but-1′-enyl-2-methyl-4-oxo*cyclo*hex-2-enecarboxylate (15·1 g., 3%) was isolated by filtration. A black carbonaceous residue remained in the distillation flask.

Isolation of 5-Methylsorbic Acid from the Mixture M.—The mixture M (see above, 9·1 g.) was stirred at 20° with sodium hydroxide (2·3 g.) in water (46 ml.) for 20 hr. Unhydrolysed ester was extracted with ether and isolated (6·5 g., 71·5%) by evaporation. On distillation, methyl 4 : 5-dihydro-2 : 4 : 4-trimethyl-5-methylene-3-furoate (5·7 g., 63%: purity checked by infrared spectrum), b. p. 93—95°/22 mm., n_D^{22} 1·4819, was obtained (Found: C, 66·05; H, 7·95%).

The aqueous-alkaline solution was acidified (no effervescence) and extracted with ether. The ethereal extracts were themselves extracted with sodium hydroxide solution and evaporation of the ethereal layer showed that no ketone was present. The alkaline solution was acidified and extracted with ether to give crude 5-methylsorbic acid (2·0 g., 24·5%). A portion of the crude acid (0·25 g.) was esterified with diazomethane and distilled (n_D^{23} 1·5113): examination of its infrared spectrum showed it to be virtually pure methyl 5-methylsorbate (below). The remainder of the crude acid (1·75 g.) was crystallised twice from aqueous ethanol, to give pure 5-*methylsorbic acid* (1·4 g., 20%), plates, m. p. 113° (Found: C, 66·8, 66·45; H, 8·3, 8·0. $C_7H_{10}O_2$ requires C, 66·7; H, 8·0%). The acid sublimed in needles at 0·2 mm. Its p-*bromophenacyl ester*, m. p. 121°, crystallised from aqueous ethanol (Found: C, 55·7; H, 4·7. $C_{15}H_{15}O_3Br$ requires C, 55·7; H, 4·9%).

5-Methylsorbic acid absorbed 2 mol. of hydrogen over 5% palladium–barium sulphate in ethyl acetate, and the p-*bromophenacyl ester* of the liquid product, 5-methylhexanoic acid, had m. p. 77°, undepressed by a specimen prepared from authentic acid (m. p. 76°) (Found: C, 55·2; H, 6·0. $C_{15}H_{19}O_3Br$ requires C, 55·0; H, 5·8%). The p-*phenylphenacyl* ester of the hydrogenation product had m. p. 78° (Found: C, 77·5; H, 7·8. $C_{21}H_{24}O_3$ requires C, 77·75; H, 7·5%). It depressed the m. p. of the *p*-phenylphenacyl ester (m. p. 74—75°) of 4 : 4-dimethylpentanoic acid to 58—63°.

Pure 5-methylsorbic acid gave, on treatment with diazomethane, the *methyl ester*, b. p. 92°/20 mm., n_D^{23} 1·5139 (Found: C, 68·1; H, 8·75. $C_8H_{12}O_2$ requires C, 68·5; H, 8·6%), $\lambda_{max.}$ 272 mμ (ε 27,000), $\nu_{max.}$ 1709 (α-unsaturated CO_2Me) and 1634 and 1609 cm.$^{-1}$ (conjugated diene).

In an identical hydrolysis of mixture M, in which stirring was continued for only 5½ hr., 7·2 g. (79%) of unhydrolysed ester were obtained. On distillation, this gave methyl 4 : 5-dihydro-2 : 4 : 4-trimethyl-5-methylene-3-furoate (6·7 g., 73·5%), b. p. 95—97°/23 mm., n_D^{24} 1·4825. From the alkaline solution 5-methylsorbic acid (1·8 g., 22%) was obtained, having m. p. 112° after crystallisation (1·3 g., 16%). The dihydrofuroate (6·2 g.) when boiled for 90 min. with potassium hydroxide (2·5 g.) in methanol (30 ml.) gave unchanged ester (2 g.) and the corresponding acid (3 g.), m. p. 124° after crystallisation.

Treatment of Mixture M with Methyl Sodioacetoacetate.—Mixture M (9·1 g.) was heated under reflux for 16 hr. with methyl sodioacetoacetate [from sodium (1·3 g.), methyl acetoacetate (5·8 g.), and dry methanol (50 ml.)]. The product was poured into water and separated into acidic (0·91 g.) and neutral material. The latter, on distillation, gave a product (7·2 g.) of b. p. 94—100°/22 mm., n_D^{28} 1·4840 (ferric chloride test negative). The residue from this distillation (approx. 100 mg.) gave no methyl 6-*iso*but-1′-enyl-2-methyl-4-oxo*cyclo*hex-2-enecarboxylate even after prolonged cooling and seeding.

Reaction between Methyl Sodioacetoacetate (2 Mol.) and 3-Chloro-3-methylbutyne (1 Mol.) in Refluxing Methanol.—3-Chloro-3-methylbut-1-yne (38·5 g., 0·375 mole) was added dropwise to a stirred and refluxing solution of methyl sodioacetoacetate [made from sodium (17·2 g., 0·75 g.-atom), methyl acetoacetate (87 g., 0·75 mole), and dry methanol (250 ml.)], and the mixture was stirred on a steam-bath for 22 hr. Most of the methanol was removed by distillation and the residue was poured into water (300 ml.), just acidified with mineral acid, and

XUM

extracted with ether. The ethereal extracts were dried, evaporated, and fractionally distilled, thirteen fractions being collected and examined spectroscopically (ultraviolet and infrared).

After elimination of a small fore-run, methyl 4 : 5-dihydro-2 : 4 : 4-trimethyl-5-methylene-3-furoate (49·2 g., 71%) was isolated; it had b. p. 92—101°/~15 mm., n_D^{20} 1·4810—1·4820. The infrared spectrum showed none of the characteristic bands of methyl 5-methylsorbate. The next fractions, b. p. 96—108°/~0·5 mm., n_D^{20} 1·4724—1·4776 (7·5 g.), showed hydroxylic infrared absorption and scrutiny indicated that methyl 4 : 5-dihydro-5-hydroxy-2 : 4 : 4 : 5-tetramethyl-3-furoate was present in the mixture (see below). Following these, material of b. p. 108—118°/~0·5 mm. was isolated (17·7 g.): this partly crystallised and from it pure methyl 6-*iso*but-1′-enyl-2-methyl-4-oxo*cyclo*hex-2-enecarboxylate (7·6 g., 9·1%) was obtained. The uncrystallisable viscous residue gave a purple-red ferric reaction. Finally, two fractions boiling erratically near 122°/~0·5 mm., n_D^{20} 1·5147, $\lambda_{max.}$ 228 mμ (ε 8200) (1·0 g.), and n_D^{20} 1·5238, $\lambda_{max.}$ 225 mμ (ε 7750) (0·7 g.), were isolated. Both showed hydroxylic infrared absorption and gave purple-red ferric colours. When united and refractionated, a little more of the crystalline *cyclo*hexenone was isolated, but no other component could be obtained pure.

In a second experiment the results were similar, though the dihydrofuroate contained small quantities of methyl 5-methylsorbate.

Reaction between Methyl Sodioacetoacetate (1 *Mol.*) *and* 3-*Chloro*-3-*methylbutyne* (2 *Mol.*) *in Refluxing Methanol.*—3-Chloro-3-methylbut-1-yne (51·5 g., 0·5 mole) was added dropwise to a stirred, refluxing solution of methyl sodioacetoacetate [from sodium (5·75 g., 0·25 g.-atom), methyl acetoacetate (29 g., 0·25 mole), and methanol (250 ml.)], and the mixture was stirred on a steam-bath for 20 hr. Most of the methanol was distilled off, and water (300 ml.) was added. The organic layer was isolated with ether and distilled. After elimination of material of b. p. 52—88°/12 mm. (1·18 g.), n_D^{20} 1·4314, the following fractions were taken: (i) b. p. 88—106°/12 mm. (1·00 g.), n_D^{20} 1·4612; (ii) b. p. 106—110°/12 mm. (1·74 g.), n_D^{20} 1·4672, $\lambda_{max.}$ 250 mμ (ε 8000); (iii) b. p. 66—86°/0·2 mm. (2·60 g.), n_D^{20} 1·4668, $\lambda_{max.}$ 250 mμ (ε 7500); (iv) b. p. 86—104°/0·2 mm (2·53 g.), n_D^{20} 1·4906, $\lambda_{max.}$ 233 mμ (ε 7000). Infrared spectra, run on all fractions, showed that (ii) was almost pure methyl 4 : 5-dihydro-5-methoxy-2 : 4 : 4 : 5-tetramethyl-3-furoate (see below), and that (i) and (iii) contained material of slightly lower purity. From fraction (iv), methyl 6-*iso*but-1′-enyl-2-methyl-4-oxo*cyclo*hex-2-enecarboxylate (m. p. and mixed m. p. 72°) separated during some days.

Methyl 4 : 5-dihydro-2 : 4 : 4-trimethyl-5-methylene-3-furoate (1 g.), 3-chloro-3-methylbutyne (1 g.), and dry methanol (25 ml.) were heated under reflux for 4 hr. The methanol and excess of chloro-compound were removed by evaporation and the residue distilled to give pure methyl 4 : 5-dihydro-5-methoxy-2 : 4 : 4 : 5-tetramethyl-3-furoate (infrared spectrum) in almost quantitative yield.

Methyl 4 : 5-*Dihydro*-2 : 4 : 4-*trimethyl*-5-*methylene*-3-*furoate* (I).—Under the usual acidic conditions, the dihydromethyleuefuran formed a yellow-orange *bis*-2 : 4-*dinitrophenylhydrazone*, m. p. 232° (decomp.) (from methyl cellosolve) (Found: C, 47·5; H, 4·55; N, 20·2. $C_{22}H_{24}O_{10}N_8$ requires C, 47·15; H, 4·35; N, 20·0%), $\lambda_{max.}$ 360 mμ (ε 43,500) (in chloroform).

Ozonolysis of Methyl 4 : 5-*Dihydro*-2 : 4 : 4-*trimethyl*-5-*methylene*-3-*furoate.*—The ester (1·82 g.) in glacial acetic acid (50 ml.) was treated at 10° with 4—5% ozonised oxygen, the product added to zinc dust (3 g.) and water (50 ml.), and the mixture steam-distilled. The distillate (250 ml.) was neutralised, and dimedone (3 g.) in 50% aqueous ethanol (100 ml.) added: the mixture was set aside (18 hr.). The crystalline product which separated (950 mg., 35%) had m. p. 190°, undepressed by the dimedone derivative of formaldehyde.

In another experiment the ozonolysis was carried out at 0° in carbon tetrachloride solution, and the ozonide decomposed by water. The organic layer was separated, washed, dried, and evaporated to give an oil which reacted vigorously with warm 10% alcoholic potassium hydroxide (15 ml.) and was then heated under reflux for 1 hr. The product was evaporated, diluted with a little water, and acidified. An acid was precipitated which, crystallised from benzene, had m. p. 186—188° (vigorous effervescence) undepressed on admixture with dimethylmalonic acid.

4 : 5-*Dihydro*-2 : 4 : 4-*trimethyl*-5-*methylene*-3-*furoic Acid.*—The corresponding methyl ester (19·6 g.) was heated under reflux with 10% alcoholic potassium hydroxide (50 ml.) for 6 hr. Most of the ethanol was distilled off and water (100 ml.) was added. A little unhydrolysed material was removed with ether, and the purple aqueous solution was warmed to expel dissolved solvent, cooled to 0°, and just acidified (the purple colour disappeared sharply near

neutrality point). The precipitated **4 : 5-*dihydro*-2 : 4 : 4-*trimethyl*-5-*methylene*-3-*furoic acid***, m. p. 122°, was filtered off and recrystallised from light petroleum (b. p. 60—80°), then having m. p. 124—125° (10 g.) (Found: C, 64·6; H, 7·4%; equiv., 168. $C_9H_{12}O_3$ requires C, 64·3; H, 7·2%; equiv., 168), $\lambda_{max.}$ 263 mμ (ε 12,000), $\nu_{max.}$ (mull) 1691 m, 1675 s (bonded and α-unsaturated CO_2H), 1649 s and 892 m ($CH_2{:}C<$), and 1620 s cm.$^{-1}$ (conjugated C=C). The acid was reconverted by diazomethane into the methyl ester, b. p. 92°/20 mm., $n_D^{19\cdot5}$ 1·4830, whose infrared spectrum was identical with that of the ester mentioned earlier.

Oxidation of **4 : 5-*Dihydro*-2 : 4 : 4-*trimethyl*-5-*methylene*-3-*furoic Acid with Permanganate***.—The acid (10 g.) was added to water (100 ml.) and neutralised with potassium hydroxide. Potassium permanganate (20 g.) was added with vigorous stirring, at <35°. The mixture was stirred for 18 hr., then filtered, and the manganese dioxide was washed. The filtrate and washings were concentrated to 100 ml., acidified (much carbon dioxide evolved), and continuously extracted with ether. Cautious evaporation of the ether left an oil which was distilled at 40° *in vacuo*, the volatile product being collected in a cold trap. This formed a *p*-bromophenacyl ester, m. p. 84°, undepressed when admixed with authentic *p*-bromophenacyl acetate.

The white solid remaining from the distillate crystallised from light petroleum, then having m. p. 78—79° [Found: C, 58·2, 58·5; H, 8·7, 8·5; O (direct), 32·9%; equiv., 142. Calc. for $C_7H_{12}O_4$: C, 58·3; H, 8·4; O, 33·3%; equiv., 144·2], $\nu_{max.}$ (mull) 1703 and 1689 cm.$^{-1}$ (just resolved: saturated C:O and CO_2H). There was no high-intensity absorption in the ultraviolet spectrum. The **2 : 4-*dinitrophenylhydrazone*** crystallised from ethanol in yellow-orange needles, m. p. 212° after softening (Found: C, 48·05; H, 5·2; N, 16·7. $C_{13}H_{16}O_6N_4$ requires C, 48·15; H, 5·0; N, 17·3%). The semicarbazone had m. p. 190° if heated slowly and 198° on more rapid heating (all m. p.s with effervescence but without darkening). The instantaneous m. p. was 218° (Kofler hot-bar), the melting-front gradually receding. Despite the dependence of m. p. on the conditions for its determination there was a clear depression on admixture with the semicarbazone of **3 : 3**-dimethyl-4-oxopentanoic acid [18] (m. p. 198° on rapid heating: instantaneous m. p. 208—210°) but none with the semicarbazone of **2 : 2**-dimethyl-4-oxopentanoic acid.[19] The identity and non-identity were confirmed by comparison of infrared spectra.

3 : 3-*Dimethylhexane*-2 : 5-*dione*.—**4 : 5**-Dihydro-**2 : 4 : 4**-trimethyl-5-methylene-3-furoic acid (9 g.) was heated to 90° for 15 min. with 2N-sulphuric acid (30 ml.). Carbon dioxide was evolved, the suspended acid disappeared, and a liquid layer was formed. After saturation with salt, the solution was extracted with ether, and the extracts were washed with brine dried, and evaporated. Distillation gave **3 : 3-*dimethylhexane*-2 : 5-*dione*** (3 g.), b. p. 77—78°/10 mm., n_D^{20} 1·4380 (Found: C, 67·6; H, 10·2. $C_8H_{14}O_2$ requires C, 67·55; H, 9·9%), $\nu_{max.}$ 1715 cm.$^{-1}$ (strong; saturated ketone). The *disemicarbazone* had m. p. 205—206° (decomp.) (from aqueous ethanol) (Found: C, 47·6; H, 8·1; N, 32·4. $C_{10}H_{20}O_2N_6$ requires C, 46·9; H, 7·8; N, 32·8%). The orange-yellow ***bis*-2 : 4-*dinitrophenylhydrazone*** crystallised from methyl cellosolve in needles, m. p. 217—218° (Found: C, 47·95; H, 4·65; N, 21·8. $C_{20}H_{22}O_8N_8$ requires C, 47·95; H, 4·4; N, 22·1%).

Patrick reports b. p. 93°/20 mm., n_D^{25} 1·4363, for **3 : 3**-dimethylhexane-**2 : 5**-dione but made no derivatives.[20]

Oxidation of **3 : 3-*Dimethylhexane*-2 : 5-*dione* with *Hypochlorite***.—The diketone gave a strong iodoform reaction. It (2 g.) was added to excess of sodium hypochlorite (10—14% w/v) during 1 hr. and stirred for a further 2 hr. Sodium hydrogen sulphite was added to remove the hypochlorite, and the acidified solution was boiled to expel sulphur dioxide. The solution was then thoroughly extracted with ether, and the extracts were evaporated to a brown oil (500 mg.) from which crystals separated. The latter, recrystallised from concentrated hydrochloric acid, had m. p. 141·5—142° alone or mixed with **1 : 1**-dimethylsuccinic acid (m. p. 142·5—143·5°) prepared from ethyl 2-cyano-3-methylbut-2-enoate and potassium cyanide.

Base-catalysed Cyclisation of **3 : 3-*Dimethylhexane*-2 : 5-*dione***.—The dione (9 g.) was heated in 2% aqueous sodium hydroxide under reflux for 20 min., the opalescent pink solution becoming clear. The solution was saturated with salt and extracted thoroughly with ether. Drying, evaporation, and distillation at 12 mm. gave a fraction (6·3 g.), b. p. 74—76°, n_D^{20} 1·4666—1·4688,

[18] Baumgarten and Gleason, *J. Org. Chem.*, 1951, **16**, 1658.
[19] Lapworth, *J.*, 1904, 1214.
[20] Patrick, *J. Org. Chem.*, 1952, **17**, 1269.

containing 3 : 4 : 4- and 3 : 5 : 5-trimethyl*cyclo*pent-2-enone [2] (Found: C, 77·4; H, 9·6. Calc. for $C_8H_{12}O$: C, 77·35; H, 9·75%), $\lambda_{max.}$ 226 mμ (ε 11,400), $\nu_{max.}$ 1710 s (unsaturated 5-ring ketone) and 1634 m cm.$^{-1}$ (conjugated ·C=C·). The product gave a 2 : 4-dinitrophenylhydrazone, m. p. 163° undepressed by that formed in the baryta-hydrolysis experiment reported below (Found: C, 55·7; H, 5·7%). The semicarbazone had m. p. 171—173° (decomp.) (Found: C, 59·1; H, 8·3. $C_9H_{15}ON_3$ requires C, 59·6; H, 8·3%).

The *cyclo*pentenone product (2 g.) was stirred with water (50 ml.), and potassium permanganate (8 g.) added during 2 hr., at <35°. Stirring was continued for 18 hr. and the manganese dioxide filtered off and washed. The filtrate and washings were concentrated to 35 ml. and a portion (15 ml.) was acidified (carbon dioxide evolved). The solution was neutralised and semicarbazide hydrochloride (300 mg.) and sodium acetate (500 mg.) were added. After 18 hr. crystals (100 mg.) were filtered off and recrystallised from water; they had m. p. 183·5°, raised by further crystallisation to 187—188° (slow heating). The semicarbazone, which melted with decarboxylation, depressed the m. p. of the semicarbazone of 3 : 3-dimethyl-4-oxopentanoic acid but not that of the semicarbazone of 2 : 2-dimethyl-4-oxopentanoic acid. Identity was confirmed by infrared spectra.

Baryta-hydrolysis of an Ethyl Ester Similar to M.—The ethyl ester (47 g.) obtained in an experiment similar to that described for mixture M was stirred under reflux with barium hydroxide octahydrate (60 g.) in water (1 l.) for 72 hr. After cooling and acidification (not excess), the mixture was extracted with ether, and the extracts were dried, evaporated, and distilled at 10 mm. to give a product (14 g.), b. p. 80—94°, n_D^{20} 1·4574—1·4535. Two redistillations (10 mm.) gave the following materials: (i) b. p. 72—74°, n_D^{20} 1·4602—1·4592 (4·5 g.), $\lambda_{max.}$ 226 mμ (ε 11,500); (ii) b. p. 74—75°, n_D^{20} 1·4572 (2·0 g.); (iii) b. p. 75—76°, n_D^{20} 1·4562 (2·0 g.). Fraction (i) gave an orange 2 : 4-dinitrophenylhydrazone, m. p. 163° (from ethanol) (Found: C, 54·7; H, 5·2. Calc. for $C_{14}H_{16}O_4N_4$: C, 55·25; H, 5·3%), $\lambda_{max.}$ 381 mμ (ε 25,800).

The residue in the flask after the original distillation solidified, and on crystallisation gave 5-methylsorbic acid, m. p. and mixed m. p. 112° (*p*-bromophenacyl ester, m. p. and mixed m. p. 121°).

4 : 5-*Dihydro*-2 : 4 : 4 : 5-*tetramethyl*-3-*furoic Acid.*—4 : 5-Dihydro-2 : 4 : 4-trimethyl-5-methylene-3-furoic acid (0·324 g.) was hydrogenated in ethanol over 5% palladium–barium sulphate (1·1 mol. of hydrogen absorbed). The *product*, crystallised from light petroleum (b. p. 60—80°), had m. p. 95·5—96°, undepressed by the specimen below (Found: C, 63·5; H, 8·5%; equiv., 167. $C_9H_{14}O_3$ requires C, 63 5; H, 8·3%; equiv., 170), $\lambda_{max.}$ 254 mμ (ε 11,200).

Ethyl 4 : 5-dihydro-2 : 4 : 4-trimethyl-5-methylene-3-furoate was similarly hydrogenated [1·02 mol. of hydrogen absorbed: uptake slow (48 hr.)]; the product, b. p. 86°/10 mm., n_D^{20} 1·4680, had $\lambda_{max.}$ 256 mμ (ε 10,150 in ethanol) which was not altered after 24 hr. in approx. 0·01N-ethanolic alkali. In chloroform the max. was at 257 mμ (ε 10,050). There were two strong infrared bands, at 1694 and 1630 cm.$^{-1}$. On hydrolysis with 10% alcoholic potassium hydroxide (15 hr. under reflux) the above acid (m. p. and mixed m. p. 95·5—96°) was obtained.

Methyl 4 : 5-*Dihydro*-5-*methoxy*-2 : 4 : 4 : 5-*tetramethyl*-3-*furoate* (IX).—Methyl 4 : 5-dihydro-2 : 4 : 4-trimethyl-5-methylene-3-furoate (3 g.) was added to dry methanol (20 ml.) containing concentrated sulphuric acid (5 drops). The mixture became warm and was set aside for 18 hr. Alcoholic potassium hydroxide was added to neutrality. The mixture was filtered and evaporated. The residue was extracted with ether, washed, dried, evaporated, and distilled to give *methyl* 4 : 5-*dihydro*-5-*methoxy*-2 : 4 : 4 : 5-*tetramethyl*-3-*furoate* (2 g.), b. p. 104—106°/10 mm., n_D^{20} 1·4683—1·4688 (Found: C, 61·6; H, 8·45. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·4%), $\lambda_{max.}$ 250 mμ (ε 10,900 in ethanol), 251 mμ (ε 10,800 in chloroform). In alcoholic N/100-potassium hydroxide the max. was at 250 mμ (ε 9400) soon after dissolution and at 253 mμ (ε 7400) after 4 and 24 hr. There were infrared bands at 1736 w, 1695 s (α-unsaturated ester) and 1639 s cm.$^{-1}$ (conjugated ·C=C·). The origin of the weak band at 1736 cm.$^{-1}$ is uncertain: it is not removed by treatment with potassium borohydride. The methoxy-compound formed the bis-2 : 4-dinitrophenylhydrazone, m. p. 232° (decomp.), mentioned above (mixed m. p. and infrared comparison).

Methyl 4 : 5-*Dihydro*-5-*hydroxy*-2 : 4 : 4 : 5-*tetramethyl*-3-*furoate* (*tautomeric mixture* X ⇌ XII).—(a) *From condensations between* 3-*chloro*-3-*methylbutyne and methyl sodioacetoacetate worked up under slightly acid conditions.* The fractions lying between those containing the dihydromethylenefuran with methyl 5-methylsorbate and the crystalline *cyclo*hexenone

(b. p. in one case 65—97°/0·02 mm.) were repeatedly distilled, the composition being followed by the hydroxylic infrared absorption. The *dihydrohydroxyfuran* had b. p. 71°/0·1 mm., n_{16}^{D} 1·4561, and gave no colour with ferric chloride even after 7 days in the reagent (Found: C, 60·5; H, 8·35. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·05%). It was not hydrogenated in ethyl acetate over 25% palladium–carbon, 10% palladium–barium sulphate, or Adams platinum catalyst. In the presence of the last catalyst, with glacial acetic acid as solvent, 2·02 mol. of hydrogen were absorbed. The dihydrohydroxyfuran had $\lambda_{max.}$ 250 mμ shifted to 278 mμ in approx. 0·01N-ethanolic alkali. Its infrared spectrum was identical with that of the specimen below. Under the usual conditions, a yellow-orange bis-2 : 4-dinitrophenylhydrazone was formed, having m. p. 235° (decomp.) (bath), 248° (decomp.) (Kofler hot-bar), after crystallisation from methyl cellosolve, washing with methanol, and drying at 100°/0·02 mm. (Found: C, 47·45; H, 4·55; N, 20·15), $\lambda_{max.}$ (in chloroform) 360 mμ (ε 43,500), $\nu_{max.}$ 1742 cm.$^{-1}$ (·CO_2Me). The derivative was identical (mixed m. p. and infrared trace) with the bis-2 : 4-dinitrophenylhydrazone from methyl 4 : 5-dihydro-2 : 4 : 4-trimethyl-5-methylene-3-furoate and from methyl 4 : 5-dihydro-5-methoxy-2 : 4 : 4 : 5-tetramethyl-3-furoate.

(b) *From methyl* 4 : 5-*dihydro*-2 : 4 : 4-*trimethyl*-5-*methylene*-3-*furoate*. This substance (3 g.) was shaken at 20° with 5% aqueous sulphuric acid (25 ml.) for 3 hr. The product was extracted with ether, and the extract was dried (Na_2SO_4), evaporated, and distilled, to give the hydroxy-compound (2·64 g.), b. p. 72—73°/0·07 mm., n_D^{19} 1·4550 (Found: C, 60·45; H, 8·1%), $\lambda_{max.}$ 252 mμ (ε 2200 in ethanol); in 0·01N-ethanolic alkali a double max. developed at 252 and 280 mμ and the former gradually subsided leaving, after 4 hr., the max. at 280 mμ (ε 2200). The spectrum shows other interesting variations with time which are being examined.

The hydroxy-compound (300 mg.), methanol (5 ml.), and 1 small drop of sulphuric acid were set aside for 2 days at 20°, then poured into water. The product was isolated with ether; its infrared spectrum was identical with that of the methoxy-compound (IX).

4-*Ethyl*-4 : 5-*dihydro*-2 : 4-*dimethyl*-5-*methylene*-3-*furoic Acid*.—3-Chloro-3-methylpentyne (40 g.; b. p. 105°, n_D^{20} 1 4330) was added to a refluxing solution of ethyl sodioacetoacetate (10% excess) from sodium (8·4 g.), ethyl acetoacetate (48 g.), and methanol (170 ml.), and the mixture was heated and stirred for 15 hr. The product was worked up in the usual way and gave an *ester*, b. p. 95—96°/10 mm., n_D^{20} 1·4823 (27·5 g., 41%) (Found: C, 67·3; H, 8·1. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%), $\lambda_{max.}$ 267 mμ (ε 12,000). From the analytical data it appears to be methyl 4-ethyl-4 : 5-dihydro-2 : 4-dimethyl-5-methylene-3-furoate containing little, if any, material arising from γ-attack. The ester (1·97 g.), when ozonised in glacial acetic acid (50 ml.) as described above, gave formaldehyde dimedone derivative (1·4 g., 56%), m. p. and mixed m. p. 190°. The ester (19·6 g.) was heated under reflux for 6 hr. with 10% alcoholic potassium hydroxide (60 ml.). Working up as previously described gave 4-*ethyl*-4 : 5-*dihydro*-2 : 4-*dimethyl*-5-*methylene*-3-*furoic acid* (15 g., 83%), m. p. 107—108° [from light petroleum (b. p. 40—60°)] (Found: C, 65·9; H, 7·6. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%), $\lambda_{max.}$ 265 mμ (ε 11,500). There were infrared bands at 1698 m, 1669 s (bonded α-unsaturated CO_2H), 1647 s and 900 m (CH_2=C<), and 1621 s cm.$^{-1}$ (conjugated ·C=C·). When warmed with 2N-sulphuric acid (20 ml.) for 20 min., the acid (2·2 g.) gave, after extraction and working up, 3-*ethyl*-3-*methylhexane*-2 : 5-*dione* (1·2 g., 80%), b. p. 102°/10 mm., n_D^{20} 1·4433 (Found: C, 68·75; H, 10·5. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%).

Reaction between Ethyl Sodioacetoacetate and 3-*Chlorobutyne*.—3-Chlorobutyne (21·6 g., 0·24 mole) was heated under reflux for 30 hr. with ethyl sodioacetoacetate prepared from sodium (6·2 g., 0·27 g.-atom), ethyl acetoacetate (35·1 g., 0·27 mole), and dry ethanol (110 ml.). Much of the ethanol was distilled off, and the residue was poured into water and worked up in the usual way. Distillation gave a fore-run (0·9 g.), b. p. 90°/15 mm., n_D^{20} 1·4559, giving a faint ferric chloride reaction. Fractions (showing no ferric reaction) were then taken as follows: (*a*) b. p. 100—104°/15 mm., n_D^{20} 1·4772 (3·8 g.), $\lambda_{max.}$ 264 mμ ($E_{1\,cm.}^{1\%}$ 535); (*b*) b. p. 104—106°/15 mm., n_D^{20} 1·4753 (3·3 g.), $\lambda_{max.}$ 264 mμ ($E_{1\,cm.}^{1\%}$ 390); (*c*) b. p. 106—107°/15 mm., n_D^{20} 1·4712 (1·4 g.), $\lambda_{max.}$ 254 mμ ($E_{1\,cm.}^{1\%}$ 230); (*d*) b. p. 64°/0·25 mm., n_D^{20} 1·4708 (1·0 g.), $\lambda_{max.}$ 258 mμ ($E_{1\,cm.}^{1\%}$ 200); (*e*) b. p. 64—70°/0·25 mm., n_D^{20} 1·4696 (0·6 g.), $\lambda_{max.}$ 258 mμ ($E_{1\,cm.}^{1\%}$ 182); (*f*) b. p. 70—80°/0·25 mm., n_D^{20} 1·4718 (0·4 g.), $\lambda_{max.}$ 256 mμ ($E_{1\,cm.}^{1\%}$ 210). Finally material of b. p. 90—112°/0·25 mm., n_D^{20} 1·4826—1·4906 (0·55 g.), giving a ferric reaction, was isolated. The infrared spectrum of (*a*) showed it to be mainly the dihydromethylenefuran ester [bands at 1701 s (α-unsaturated ester), 1653 s (conjugated C=C–O), and 899 m cm.$^{-1}$ (CH_2:C)]. There was only a small band at 1587 cm.$^{-1}$ indicative of ethyl 2 : 4 : 5-trimethyl-3-furoate. The

intensity of the last band increased in the higher fractions whilst the band at 899 cm.$^{-1}$ disappeared. Fractions (*c*)—(*f*) were nearly pure furoic ester. The terminal acetylenic vibration was negligible in (*a*)—(*f*).

In a similar experiment, with methanol as solvent and a reflux period of 15 hr., methyl ester, b. p. 94—100°/12 mm., n_D^{20} 1·4790—1·4773 (76%), was isolated. A redistilled sample had b. p. 96—98°/12 mm., n_D^{20} 1·4792 (Found: C, 64·4; H, 6·9. Calc. for $C_9H_{12}O_3$: C, 64·3; H, 7·2%). On ozonolysis the formaldehyde dimedone derivative (26%; m. p. and mixed m. p. 190°) was obtained. The ester (16·8 g.) was heated under reflux for 2 hr. with 10% alcoholic potassium hydroxide (60 ml.). Most of the solvent was distilled off, the residue was diluted with water, and a little unchanged ester removed with ether. The aqueous solution was warmed to expel dissolved ether, cooled to 0°, and acidified. An oil separated and rapidly solidified, to give crude 2 : 4 : 5-trimethyl-3-furoic acid (14 g.). Crystallised from 40% aqueous acetic acid (400 ml.; charcoal) it gave pure acid (10 g.), m. p. 132—133°, undepressed by an authentic specimen kindly supplied by Professor Reichstein.[16] There were infrared bands at 1667 (broad), s (conjugated CO_2H), 1629 s, and 1576 s (furan). The ultraviolet max. was at 258 mμ (ε 3700).

The acid (1·54 g.), with diazomethane in ether, gave the methyl ester (1·3 g.), b. p. 104°/10 mm. The ethyl ester, prepared by esterification with diazoethane, had infrared bands at 1709 s (conjugated ester), 1642 w, 1585 s (furan band), and no absorption near 899 cm.$^{-1}$; the infrared spectrum closely simulated that of fractions (*c*)—(*f*) but was very different from that of (*a*); the ultraviolet max. was at 259 mμ (ε 3300).

Reaction between Methyl Sodioacetoacetate and 3-*Chloropropyne.*—The usual reaction was carried out, with 3-chloropropyne (37 g.) and methyl sodioacetoacetate [from sodium (12·6 g.), ethyl acetoacetate (71·5 g.), and dry methanol (250 ml.)]. After being stirred at 20° for 7 hr. the mixture was heated under reflux for 15 hr. and worked up and distilled in the usual way. The product was difficult to separate and only a central cut, b. p. 92—95°/10 mm., n_D^{20} 1·4878—1·4882 (6 g.), was examined. It had an ultraviolet max. at 260 mμ (ε 3230). On ozonolysis it yielded formaldehyde dimedone derivative (13%; m. p. and mixed m. p. 190°). The ester (2 g.) was hydrolysed by refluxing it for 2 hr. with potassium hydroxide (0·82 g.) in water (2 ml.) and ethanol (8 ml.); the acid (approx. 1 g.), isolated in the usual way, had m. p. 136—137° [from light petroleum (b. p. 60—80°)] and did not depress the m. p. of authentic 2 : 5-dimethyl-3-furoic acid.[17] The acid showed a strong broad band at 1678 (conjugated CO_2H) and bands at 1637 m, 1615 w, and 1582 s cm.$^{-1}$ (furan). The ethyl ester, prepared by diazoethane, had bands at 1709 s (furan CO_2Me), 1623 w, and 1592 s cm.$^{-1}$ (furan).

In a second experiment involving a reflux period of 30 hr., with ethanol as solvent, the product was isolated and distilled through a helix-packed column. All the fractions were impure and contained terminal-acetylenic bands. After elimination of a ketonic fraction (strong infrared band at 1736 cm.$^{-1}$), material of b. p. 84°/9 mm., but with a large refractive index spread (n_D^{20} 1·4684—1·4808), was isolated. Bands at 1695 s (α-unsaturated CO_2Me) 1647 s (conjugated ·C=C·), and 913 m [CH_2:C(·O⁻)] cm.$^{-1}$ suggest that dihydromethylenefuran is probably present in the impure earlier cuts. In the later fractions the characteristic furan band at 1592 cm.$^{-1}$ appears clearly.

Methyl 6-iso*But*-1′-*enyl*-2-*methyl*-4-*oxo*cyclo*hex*-2-*enecarboxylate* (XIII; R = Me).—The substance separated from methanol in large, well-formed, lozenge-shaped crystals, m. p. 73°, giving no colour with ferric chloride [Found: C, 70·55, 70·1, 70·6, 70·3; H, 8·35, 8·5, 8·2, 8·1%; *M* (Rast), 222. $C_{13}H_{18}O_3$ requires C, 70·25; H, 8·15%; *M*, 222], $\lambda_{max.}$ 232 mμ (ε 13,000); in approx. 0·01N-ethanolic sodium hydroxide a new maximum appeared at 394 mμ (ε 9000, slowly declining). There were infrared bands at 1733 s (ester), 1661 s (α-unsaturated ketone), 1623 m (conjugated ·C=C·), and 851 m cm.$^{-1}$ (Me_2C:CH). On microhydrogenation (platinum in acetic acid), 3·1 mols. of hydrogen were absorbed. Methyl 2-methyl-4-oxo*cyclo*hex-2-enecarboxylate had $\lambda_{max.}$ 232 mμ (ε 11,800), shifted to 390 mμ (ε 9500) in ~0·01N-ethanolic alkali (ε declines gradually); there were infrared bands at 1728 s (ester), 1672 s (α-unsaturated ketone) and 1631 m cm.$^{-1}$ (conjugated ·C=C·).

Methyl 6-*iso*but-1′-enyl-2-methyl-4-oxo*cyclo*hex-2-enecarboxylate formed a red 2 : 4-*dinitrophenylhydrazone*, m. p. 165—166° (Found: C, 56·8; H, 5·5; N, 13·6. $C_{19}H_{22}O_8N_4$ requires C, 56·7; H, 5·5; N, 13·9%), $\lambda_{max.}$ (in chloroform) was at 385 mμ (ε 30,000). The *semicarbazone* had m. p. 186° (decomp.), $\lambda_{max.}$ 268 mμ (ε 21,000) (Found: C, 60·1; H, 7·5; N, 15·7. $C_{14}H_{21}O_3N_3$ requires C, 60·2; H, 7·6; N, 15·0%).

XUM

6-iso*But*-1′-*enyl*-2-*methyl*-4-*oxo*cyclo*hex*-2-*enecarboxylic Acid* (XIII; R = H).—Methyl 6-*iso*but-1′-enyl-2-methyl-4-oxo*cyclo*hex-2-enecarboxylate (2 g.) was heated under reflux with 2N-sodium hydroxide (25 ml.). The substance melted and a clear solution was obtained after 5 min.: slight cloudiness then developed and the solution was cooled rapidly to 20° and extracted with ether. This extract contained 5-*iso*but-1′-enyl-3-methyl*cyclo*hex-2-enone (110 mg.), $\nu_{max.}$ 1669 and 1629 cm.$^{-1}$ (Found: C, 80·6; H, 9·8%), $\lambda_{max.}$ 232 mμ (ε 13,200). The aqueous solution was just acidified at 20° and extracted with ether. Drying and evaporation at low temperature gave a pale brown gum (1·84 g.) which, after trituration with benzene–light petroleum (b. p. 60—80°), crystallised, giving the crude acid (1·4 g.), m. p. 97—102°. After recrystallisation from the same solvent, and then twice from a small volume of benzene, the *acid* had m. p. 109—110° (with effervescence) (Found: C, 68·95; H, 7·8%; equiv., 202. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·75%; equiv., 208), $\lambda_{max.}$ 232 mμ (ε 12,000), $\nu_{max.}$ 1730 s and 1626 s cm.$^{-1}$. The first $\nu_{max.}$ is assigned to the carboxyl group; the latter is unusually low for an α-unsaturated keto-grouping and it must overlie the ·C=C· str. frequency.

When esterified with diazomethane in ether, the acid gave the starting ester, m. p. and mixed m. p. 73—74° (infrared comparison).

5-iso*But*-1′-*enyl*-3-*methyl*cyclo*hex*-2-*enone* (XV).—The ester (XIII; R = Me) (2 g.) was heated under reflux for 1 hr. with 2N-sodium hydroxide (25 ml.), then extracted with ether, and the extract was dried, evaporated, and distilled to give 5-iso*but*-1′-*enyl*-3-*methyl*cyclo*hex*-2-*enone* (1·12 g.), b. p. 81—82°/0·6 mm., $n_D^{21\cdot5}$ 1·5033 (Found: C, 80·5; H, 10·0. $C_{11}H_{16}O$ requires C, 80·45; H, 9·85%), $\lambda_{max.}$ 230 mμ (ε 13,100), $\nu_{max.}$ (liquid film) 1672 s (α-unsaturated ketone) and 1631 m cm.$^{-1}$ (α-double bond). On its microhydrogenation in acetic acid over a platinum catalyst 2·8 mols. of hydrogen were absorbed. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in red, flat needles with a golden sheen, m. p. 120° after softening (melt clear 122°) (Found: C, 59·5; H, 5·7; N, 16·0. $C_{17}H_{20}O_4N_4$ requires C, 59·3; H, 5·85; N, 16·25%), $\lambda_{max.}$ (in chloroform) 387 mμ (ε 30,200).

The ketone was also made by keeping 6-*iso*but-1′-enyl-3-methyl-4-oxo*cyclo*hex-2-enecarboxylic acid (500 mg.) above its m. p. until effervescence ceased, and then distilling the residue. The specimen (350 mg.) had b. p. 78°/0·1 mm., n_D^{19} 1·5002—1·5029 (Found: C, 80·65; H, 9·75%), $\lambda_{max.}$ 232 mμ (ε 11,000). Besides the infrared bands at 1671 and 1633 cm.$^{-1}$ there was one at 1718 cm.$^{-1}$ (saturated C:O): except for the latter, the spectrum closely resembled that of the ketone made under basic conditions.

3-Methyl*cyclo*hex-2-enone has $\lambda_{max.}$ 232 mμ (ε 13,500), unaffected by dilute alkali, and $\nu_{max.}$ 1677 s and 1626 m cm.$^{-1}$.

3-iso*Butyl*-5-*methyl*cyclo*hexanone* (XVI).—5-*iso*But-1′-enyl-3-methyl*cyclo*hex-2-enone (0·89 g.) was hydrogenated in ethyl acetate solution over palladium–carbon (absorption 263 ml. at 23°/765 mm.; 2 mol. = 261 ml.). Removal of the catalyst, evaporation, and distillation gave 3-iso*butyl*-5-*methyl*cyclo*hexanone* (780 mg.), b. p. 65°/0·1 mm., n_D^{17} 1·4513 (Found: C, 78·85; H, 12·2. $C_{11}H_{20}O$ requires C, 78·5; H, 12·0%). The ketone had no high-intensity ultraviolet absorption. On microhydrogenation in acetic acid with Adams platinum catalyst a further 0·95 mol. of hydrogen was absorbed. The 2 : 4-*dinitrophenylhydrazone* crystallised in yellow-orange needles (from ethanol), m. p. 141° (Found: C, 58·6; H, 6·95; N, 16·15. $C_{17}H_{24}O_4N_4$ requires C, 58·6; H, 6·95; N, 16·1%).

An independent specimen was made as follows.[21] *iso*Valeraldehyde (8·6 g.), ethyl acetoacetate (26 g.), and piperidine (1 g.) were mixed with water-cooling, and the product was heated at 100° for 2 hr. Sodium sulphate (anhydrous) was added to bind the water and the crude diethyl 2-*iso*butyl-4-methyl-6-oxo*cyclo*hex-4-ene-1 : 3-dicarboxylate was poured into a solution from sodium (2·3 g.) in ethanol (100 ml.). After 2 hours' refluxing most of the ethanol was distilled off and the residue was treated with water (50 ml.) and acetic acid (8 ml.) and extracted with ether. The extract was dried and evaporated (28 g.). A portion (18 g.) was distilled to give *ethyl* 6-iso*butyl*-2-*methyl*-4-*oxo*cyclo*hex*-2-*enecarboxylate* (6·7 g.), boiling mainly at 104°/0·05 mm., n_D^{24} 1·4773 (Found: C, 70·5; H, 9·4. $C_{14}H_{22}O_3$ requires C, 70·55; H, 9·3%), λ_{max} 232 mμ (ε 11,000) $\nu_{max.}$ 1730 s (ester), 1674 s (α-unsaturated ketone) and 1636 m cm.$^{-1}$ (conjugated ·C=C·). As the substance (in ethanol) gives a dirty-purple ferric reaction it probably contains some 2-oxo*cyclo*hex-3-enecarboxylate as contaminant. The other portion of diester (10 g.) was heated under reflux with water (60 ml.), sulphuric acid (7 ml.), and acetic acid (50 ml.) for 7 hr.

[21] Cf. Knoevenagel, *Annalen*, 1895, **288**, 321.

XUM

The solution was made alkaline and worked up by ether-extraction in the usual way. Distillation gave 5-*iso*butyl-3-methyl*cyclo*hex-2-enone (2·3 g.), b. p. 70—73°/0·35 mm., n_D^{17} 1·4818, $\lambda_{max.}$ 232 mμ (ε 12,000), $\nu_{max.}$ 1669 s (α-unsaturated ketone), and 1631 m cm.$^{-1}$ (conjugated •C=C•). The 2 : 4-*dinitrophenylhydrazone* formed orange-red needles, m. p. 106—107°, from ethanol (Found: C, 58·5; H, 6·4. $C_{17}H_{22}O_4N_4$ requires C, 58·95; H, 6·4%). When hydrogenated over palladium–carbon in ethyl acetate the *cyclo*hexenone (870 mg.) absorbed exactly one mol. of hydrogen. After working up and distillation (a Silicone antifoam agent was needed), 3-*iso*butyl-5-methyl*cyclo*hexanone (680 mg.), b. p. 50°/0·15 mm., n_D^{21} 1·4500, was obtained. Infrared examination showed that the product was less pure than the sample obtained by degradation, so it was purified as the 2 : 4-dinitrophenylhydrazone, which, after crystallisation from ethanol, had m. p. 142° (Found: C, 58·95; H, 7·05; N, 16·15%) and was identical (mixed m. p. and infrared spectra) with that of the degradation product described above.

Methyl 2-iso*Butyl*-6-*methyl*-4-*oxo*cyclo*hexanecarboxylate* (XIV; R = Me).—Methyl 6-*iso*but-1′-enyl-2-methyl-4-oxo*cyclo*hex-2-enecarboxylate (1·8 g.) was hydrogenated in ethyl acetate over palladium–carbon. Approx. 2 mol. of hydrogen were absorbed. After filtration, evaporation, and crystallisation from methanol, the cyclo*hexanone* (1·37 g.), m. p. 95—99° was obtained. On recrystallisation it formed thick blunt needles, m. p. 98—99·5° (Found: C, 69·1; H, 9·8. $C_{13}H_{22}O_3$ requires C, 69·0; H, 9·8%), $\nu_{max.}$ (mull) 1720 s (saturated ester) and 1710 s (saturated ketone) cm.$^{-1}$ (no strong band near 850 cm.$^{-1}$). The 2 : 4-*dinitrophenylhydrazone* crystallised from methanol in orange-yellow plates, m. p. 137° (Found: C, 56·35; H, 6·65. $C_{19}H_{26}O_6N_4$ requires C, 56·15; H, 6·45%), $\lambda_{max.}$ (in chloroform) 364 mμ (ε 25,200).

2-iso*Butyl*-6-*methyl*-4-*oxo*cyclo*hexanecarboxylic Acid* (XIV; R = H).—The foregoing ester (540 mg.) was heated under reflux (60 min.) with 2N-sodium hydroxide (10 ml.): the substance needed to be melted down from the condenser from time to time. Extraction with ether gave no neutral ketone. On acidification and extraction with ether, the aqueous phase gave the *acid* which, after crystallisation from benzene–light petroleum (b. p. 60—80°), had m. p. 140—141° without decarboxylation (m. p. after re-solidification 140—141°) (Found: C, 67·4, 67·95; H, 9·65, 9·65. $C_{12}H_{20}O_3$ requires C, 67·9; H, 9·5%). There was no high-intensity, ultraviolet light absorption. There was one rather broad, unresolved band at 1704 cm.$^{-1}$ (acid and ketone groups).

Ozonolysis of Methyl 6-iso*But*-1′-*enyl*-2-*methyl*-4-*oxo*cyclo*hex*-2-*enecarboxylate*.—The ester (300 mg.) was ozonised (2½ hr.) in " AnalaR " glacial acetic acid (8 ml.), then added to water (50 ml.) containing zinc dust (2 g.) and steam-distilled into 2 : 4-dinitrophenylhydrazine reagent. The derivative of the steam-volatile product was purified by chromatography from benzene on neutral alumina. It (300 mg.) had m. p. 127° undepressed by admixture with acetone 2 : 4-dinitrophenylhydrazone, m. p. 127°.

The Photodimer (XVIII or XIX; R = Me, R′ = CMe_2·CH).—Crystals of methyl 6-*iso*but-1′-enyl-2-methyl-4-oxo*cyclo*hex-2-enecarboxylate which had been kept in daylight were dissolved in a little methanol, and the white powder which remained was crystallised from a large volume of methanol, to give *dimethyl* 2 : 7(or 2 : 6)-*di*iso*but*-1′-*enyl*-8a : 8b(or 4*b* : 8*b*)-*dimethyl*-4 : 5(or 4 : 8)-*dioxodi*cyclo*hexano*cyclo*butane*-1 : 8(or 1 : 5)-*dicarboxylate*, needles, m. p. 248° [instantaneous m. p. (Kofler bar) 250°] [Found: C, 70·2; H, 8·4; O (direct), 22·1%; *M* (ebullioscopic), 444·5. $C_{26}H_{36}O_6$ requires C, 70·25; H, 8·15; O, 21·6%; *M*, 444·6].

The dimer was more conveniently prepared as follows. Ground crystals of the monomeric ester (3 g.) on a 3½″ Petri dish were exposed for 4 days to the light from a Hanovia ultraviolet lamp. The substance was crushed and turned over at intervals and crumbled to an extremely white powder. On crystallisation from methanol the photodimer (2·20 g.) was isolated. Evaporation of the mother-liquors and re-irradiation of the ground product gave a further quantity (0·25 g.; total yield 82%). The dimer is sparingly soluble in ether and formaldehyde methyl acetal, but soluble in chloroform and can be crystallised from benzene or methanol–chloroform. It formed a *bis*-2 : 4-*dinitrophenylhydrazone* which crystallised from a large volume of tetrahydrofuran or methyl cellosolve in yellow needles, m. p. 281° (decomp.; placed in the bath at 260°; darkened before melting). With fast heating, m. p. 287° (decomp.) was recorded. The substance was dried at 100°/0·05 mm. for 2 hr. (Found: C, 56·55; H, 5·8; N, 13·2. $C_{38}H_{44}O_{12}N_8$ requires C, 56·7; H, 5·5; N, 13·9%).

The dimer (500 mg.) was dissolved in boiling methanol (150 ml.), and potassium hydroxide (3 g.) in ethanol (25 ml.) added. After 3·5 hours' heating under reflux most of the methanol was evaporated, water was added, and a product (490 mg.), m. p. 239—248°, isolated with

chloroform. Two crystallisations raised the m. p. to 248—249° (undepressed by the starting material).

The dimer (300 mg.) was refluxed with potassium hydroxide (1 g.) in methanol (25 ml.), and benzaldehyde (1 g.) was added. Refluxing was continued for 1 hr., water added, and the *dibenzylidene derivative* filtered off and twice crystallised from methanol–chloroform; it had m. p. 210—213° [Found: C, 77·75; H, 7·45; O (direct), 15·35%; *M* (ebullioscopic), 631·1. $C_{10}H_{44}O_6$ requires C, 77·4; H, 7·15; O, 15·45%; *M*, 620·8], $\lambda_{max.}$ 295 mμ (ε 22,200), $\nu_{max.}$ 1739 s (saturated CO_2Me), 1684 s (α-unsaturated ketone), 1610 ms (conjugated •C=C•), 1594 mi, 1575 mw, 1486 m, 735 ms, 700 s, and 691 ms (various Ph vibrations), and 840 m cm.$^{-1}$ (Me_2C=CH).

Hydrogenation of the Photodimer.—The dimer (800 mg.) was hydrogenated in ethyl acetate (40 ml.) at 25% palladium–carbon. Kieselguhr was added and the mixture was filtered and concentrated to give the *diisobutyl dimer*, needles, m. p. 210° (Found: C, 69·7; H, 9·1. $(C_{13}H_{20}O_3)_2$ requires C, 69·6; H, 9·0%). In a second experiment an uptake of 2·02 mol. of hydrogen was measured and the product (75%) had m. p. 212°. There were infrared bands at 1733 s (saturated ester) and 1691 s cm.$^{-1}$ (CO α to *cyclo*butane). The band at 850 cm.$^{-1}$ had disappeared.

Ozonolysis of the Photodimer.—The dimer (500 mg.) almost all dissolved when ozonised in " AnalaR " glacial acetic acid for 90 min. The product was diluted with water and distilled into 2 : 4-dinitrophenylhydrazine reagent. After two recrystallisations the 2 : 4-dinitrophenylhydrazone [330 mg. crude; 310 mg. crystallised (equiv. to 1·2 mol. of acetone)] formed needles, m. p. 128° undepressed by authentic acetone 2 : 4-dinitrophenylhydrazone. As the sample from the ozonolysis route was slightly more orange than the authentic specimen, identity was confirmed by infrared methods.

The residue from the distillation was concentrated and set aside at 0°; this gave powdery crystals (100 mg.) of the *dimethoxycarbonyldimethyldioxocyclohexanocyclobutanedicarboxylic acid* (XVIII or XIX; R = Me, R′ = CO_2H), m. p. 309° (with effervescence and darkening) which crystallised from a large volume of ethanol–water as plates or needles (Found: C, 56·15, 56·65; H, 6·05, 6·1. $C_{20}H_{24}O_{10}$ requires C, 56·6; H, 5·7%), $\nu_{max.}$ 1723 s (bonded saturated ester), 1698 s (CO α to *cyclo*butane), and 1677 s cm.$^{-1}$ (bonded CO_2H).

Reaction Between Methyl Sodio-α-methylacetoacetate and 3-*Chloro*-3-*methylbutyne.*—The chloro-compound (34·5 g.) was added to refluxing methyl sodio-α-methylacetoacetate [from sodium (7·7 g.) and methyl α-methylacetoacetate (39 g.)] in dry methanol (150 ml.). A sample (25 ml.) was withdrawn after 30 min. and on working up and distillation gave a product having strong absorption at 274 mμ ($E^{1\%}_{1\,cm.}$ of successive fractions 810, 530, and 450). Weak allenic absorption (1950 cm.$^{-1}$) was detected in the spectrum of the middle fraction. A second sample (25 ml.), withdrawn after 2½ hr., showed similar slight allenic absorption. After boiling for 20 hr. the main material was worked up and distilled, having b. p. mainly 100—117°/21 mm., n_D^{20} 1·4768 rising to n_D^{20} 1·4860 and then falling to n_D^{20} 1·4673 (15·3 g.). The ultraviolet max. was at 274 mμ ($E^{1\%}_{1\,cm.}$ 440, equiv. to 28% of methyl 2 : 5-dimethylsorbate).

The crude ester (14·2 g.) was heated under reflux with 15% alcoholic potassium hydroxide (60 ml.) for 18 hr. and the product was then separated into neutral (1·2 g.) and acidic (9·0 g.) material. The former contained α-saturated ketonic material having a terminal acetylenic band [$\nu_{max.}$ 3242, 2112 (•C≡CH) and 1701 cm.$^{-1}$ (•C=O); 2 : 4-dinitrophenylhydrazone, m. p. 128°, $\lambda_{max.}$ 363 mμ ($E^{1\%}_{1\,cm.}$ 810)], which was not further examined. Part of the acidic product (1·0 g.) was reconverted into the methyl ester, b. p. 69—98°/20 mm., n_D^{21} 1·4810, $\lambda_{max.}$ 274 mμ ($E^{1\%}_{1\,cm.}$ 918, equiv. to 59% of methyl 2 : 5-dimethylsorbate). Crystallisation of the rest of the acidic product from light petroleum (b. p. 40—60°) gave pure 2 : 5-dimethylsorbic acid (2·85 g.), m. p. 136—137° (Found: C, 68·35; H, 8·8. Calc. for $C_8H_{12}O_2$: C, 68·5; H, 8·6%). The ultraviolet max. was at 274 mμ (ε 25,000) and the infrared spectrum was identical with that of the specimen, m. p. 137°, described by Crombie, Harper, and Sleep.[15] Its *methyl ester*, prepared by diazomethane, had n_D^{21} 1·5167 (Found: C, 70·05; H, 9·35. $C_9H_{14}O_2$ requires C, 70·1; H, 9·15%), $\lambda_{max.}$ 274 mμ (ε 24,100), $\nu_{max.}$ 1706 s (conjugated ester) and 1637 s and 1605 m cm.$^{-1}$ (conjugated diene).

The liquid residues from the crystallisation were distilled at 0·1 mm. The distillate (2 g.) solidified and when crystallisation was continued from light petroleum (b. p. 40—60°) gave 2 : 3 : 3-*trimethylpent*-4-*ynoic acid*, m. p. 81°, as needles (Found: C, 68·6; H, 8·85. $C_8H_{12}O_2$ requires C, 68·5; H, 8·6%). On microhydrogenation 1·98 mols. of hydrogen were absorbed. The methyl ester, n_D^{21} 1·4330, had bands at 3247 and 2119 (•C≡CH) and 1733 cm.$^{-1}$ (α-saturated ester).

A similar reaction was carried out at 20° for 90 min. The undistilled product had $\lambda_{max.}$ 275 mμ ($E^{1\%}_{1cm.}$ 36) but negligible infrared absorption in the allenic region.

Reaction between Methyl Sodioacetoacetate (1·0 *Mol.*) *and* 1-*Chloro*-3-*methylbuta*-1 : 2-*diene* (0·9 *Mol.*).—The chloro-compound was prepared according to the directions of Hennion *et al.*[14] and purified by fractionation through an 18″ vacuum-jacketed column packed with helices. It had b. p. 59°/15 mm., n_D^{22} 1·4751, and showed an intense allene band at 1972 cm.$^{-1}$: it was free from acetylenic absorption.

(1) *At the b. p.* 1-Chloro-3-methylbuta-1 : 2-diene (9·2 g.) was added dropwise to a refluxing solution of methyl sodioacetoacetate [from methyl acetoacetate (11·6 g.), sodium (2·3 g.), and dry methanol (50 ml.)], and refluxing was continued for 5 hr. The mixture was set aside for 48 hr., then refluxed for a further 11 hr. Most of the methanol was removed by distillation and the residue was poured into water. Isolation of the product in the usual way gave, after evaporation and rejection of a small fore-run giving a ferric chloride reaction, material of b. p. 94°/24 mm., n_D^{19} 1·4795—1·4961 (0·82 g.). This gave no ferric chloride colour, and infrared examination showed it to be a mixture containing mainly methyl 4 : 5-dihydro-2 : 4 : 4-trimethyl-5-methylene-3-furoate and methyl 5-methylsorbate in the ratio 2·2 : 1. Continuation of the distillation gave material, b. p. 73°/0·4 mm., n_D^{19} 1·5103—1·5179 (0·3 g.), giving no ferric chloride colour. No methyl *iso*but-2′-enyl-2-methyl-4-oxo*cyclo*hex-2-enecarboxylate could be isolated from this or the distillation residue.

(2) *At* 20°. The same process was carried out at 20° for 7 days. On working up, only methyl acetoacetate and 1-chloro-3-methylbuta-1 : 2-diene, identified by their infrared spectra, were isolated.

We are grateful to Dr. L. M. Jackman for the nuclear magnetic resonance data, and for his counsel on their use and interpretation. Mr. K. Maskens gave us some most useful help with certain preparations. K. Mackenzie records his debt to the D.S.I.R. for a maintenance award.

Department of Chemistry, Imperial College of Science and Technology, London, S.W.7.
King's College, Strand, London, W.C.2. [*Received, June 12th*, 1958.]

---

897. *Lipids. Part VII.* Synthesis of* 8-*Hydroxyoctadec*-cis-11- *and* -trans-11-*en*-9-*ynoic Acid: the Status of Natural* 8-*Hydroxyximenynic Acid.*

By L. Crombie and B. P. Griffin.

Fatty acids containing conjugated oxo-acetylenic groups in the centre of a long chain can be synthesised by condensing silver acetylides with half-ester acid chlorides. Dec-*cis*-3- and *trans*-3-en-1-yne are formed, in the proportion 72 : 28, when 4-toluene-*p*-sulphonyloxydec-1-yne is treated with sodamide in liquid ammonia: the mixture of geometrical isomers can be resolved by gas–liquid chromatography or fractional distillation. Employment of these hydrocarbons in the coupling procedure, followed by borohydride reduction, gives a simple synthesis of the acids named in the title, and the *trans*-stereoisomer agrees in properties with Ligthelm's description of natural 8-hydroxyximenynic acid. *cis*(unnatural)-Ximenynic acid is also synthesised.

The kernel oil of *Ximenia caffra* Sond. contains large quantities of octadec-*trans*-11-en-9-ynoic (ximenynic) acid, syntheses of which were reported in Parts II and V (ref. 4). Ligthelm further states[1] that 3—4% of an unsaturated hydroxy-acid, which he tentatively formulates as 8-hydroxyoctadec-*trans*-11-en-9-ynoic (8-hydroxyximenynic) acid, can be isolated with some difficulty. Our interest in its synthesis was aroused because it seemed

* Part VI, *J.*, 1957, 1632.

[1] Ligthelm, *Chem. and Ind.*, 1954, 249.

to be a suitable example on which to test a new approach to the construction of natural fatty acid molecules with centrally placed functional groups. This involves coupling a

$$Me\cdot[CH_2]_5\cdot CH{=}CH\cdot C{\equiv}CAg + Cl\cdot OC\cdot[CH_2]_6\cdot CO_2Me$$

$$\downarrow$$

$$(I)\ Me\cdot[CH_2]_5\cdot CH{=}CH\cdot C{\equiv}C\cdot CO\cdot[CH_2]_6\cdot CO_2Me$$

$$\downarrow$$

$$(II)\ Me\cdot[CH_2]_5\cdot CH{=}CH\cdot C{\equiv}C\cdot CH(OH)\cdot[CH_2]_6\cdot CO_2Me$$

silver acetylide with a half-ester acid chloride. Nef [2] has recorded that silver phenylacetylide reacts violently with warm benzoyl chloride to yield 1 : 3-diphenylprop-2-yn-1-one, and Davis and Scheiber [3] have recently made a useful contribution to the control of the reaction. They showed that some silver acetylides are soluble in carbon tetrachloride, chloroform, or benzene and react with simple acyl halides in such solvents to form α-acetylenic ketones.

$$Me\cdot[CH_2]_5\cdot C{\equiv}C\cdot CO\cdot[CH_2]_4\cdot CO_2R\ \ (III)$$

$$Me\cdot[CH_2]_5\cdot C{\equiv}C\cdot CH(OH)\cdot[CH_2]_4\cdot CO_2R\ \ (IV)$$

For the synthesis of 8-hydroxyximenynic acid the annexed route was followed, but first the reaction was tested on a simpler example, the synthesis of 6-hydroxydodec-7-ynoic acid. A solution of hex-1-ynylsilver in carbon tetrachloride was heated under reflux with 5-ethoxycarbonylpentanoyl chloride, to give ethyl 6-oxododec-7-ynoate (III; R = Et) in 36% yield. The latter showed the expected infrared characteristics and had an ultraviolet maximum at 222 mμ (ε 9500). It could be hydrogenated and hydrolysed to the known 6-oxododecanoic acid. On reduction with potassium borohydride, followed by hydrolysis, 6-hydroxydodec-7-ynoic acid (IV; R = H) was obtained and purified as the methyl ester. The latter was obtained in 67% overall yield from the oxo-ester (III; R = Et).

Dec-3-en-1-yne, required for the hydroxyximenynic acid sequence, has been reported earlier [4,5] as the product from treatment of 4-toluene-*p*-sulphonyloxydec-1-yne with sodamide. It has now been made in much larger quantity and this has enabled its stereochemistry to be thoroughly examined. Earlier,[4] it was pointed out that the elimination step is not necessarily stereospecific and though the hydrocarbon was successfully used for the synthesis of natural *trans*-ximenynic acid, purification procedures could have resulted in the removal of *cis*-material (for a synthesis of the latter, see below). It is now certain that this was the case, for dec-3-en-1-yne produced in the above reaction can

TABLE 1. *Dec*-cis-3- *and* -trans-3-*en*-1-*yne*.

	B. p. at 51 mm.	n_D^{25}	$\lambda_{max.}$ (mμ) [a]	Infrared: ε at 742	961 cm.$^{-1}$	Hg derivative M. p.	$\lambda_{max.}$ (mμ) [a]
cis	90—91°	1·4496	222·6 (13,590)	51	—	9·5—10·5°	247 (23,900)
trans	97·7—99·2	1·4532	221·6 (13,980)	—	119	76·5—77·5°	246·5 (29,200)

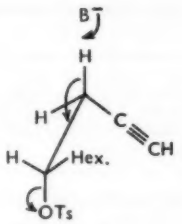
[a] ε in parentheses.

be separated into *cis*- and *trans*-components by gas–liquid chromatography. Rigorous fractional distillation of the mixture produced pure dec-*cis*-3- and -*trans*-3-en-1-yne on a preparative scale. As a check on purity, the two stereoisomers were converted into their crystalline mercury derivatives, these were purified, and the hydrocarbons regenerated

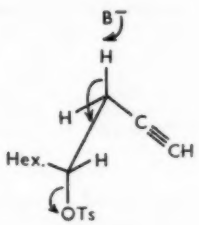
[2] Nef, *Annalen*, 1899, **308**, 277.
[3] Davis and Scheiber, *J. Amer. Chem. Soc.*, 1956, **78**, 1675.
[4] Crombie and Jacklin, *J.*, 1955, 1740; 1957, 1622.
[5] Surber, Theus, Colombi, and Schinz, *Helv. Chim. Acta*, 1956, **39**, 1299.

with no significant alteration in their constants. Ultraviolet data for the hydrocarbons are similar, but the strong bands in the infrared spectrum at 961 cm.$^{-1}$ (·CH=CH· out-of-plane deformation) for the *trans*- and at 742 cm.$^{-1}$ for the *cis*-compound, each of which is absent from the spectrum of the other stereoisomer, clearly characterise the two liquids. Data are summarised in Table 1 and the Experimental section.

If *trans*-elimination and coplanar arrangement of the four centres involved are assumed, elimination from conformations (V) and (VI), leading to *cis*- and *trans*-hydrocarbon respectively, is possible. Of the two conformations, (VI) might be expected to be the more stable with the energy difference between the two perhaps lower than usual since



(V)



(VI)

the acetylene grouping is slim and its steric effect less than that of an alkyl group. It is, however, surprising that the elimination reaction actually yields more *cis*- than *trans*-hydrocarbon (72 : 28 by infrared analysis). The result is paralleled by Allen and Whiting's finding [6] that elimination from 4-toluene-*p*-sulphonyloxypent-1-yne gives *cis*- and *trans*-pentenyne in the proportions 60—65 : 35—40. They postulate electrostatic interaction between the alkyl and the acetylene group as a stabilising factor for the transition state which gives rise to the *cis*-isomer.

With pure dec-*cis*- and -*trans*-3-en-1-yne in hand, coupling of their silver salts with 7-methoxycarbonylheptanoyl chloride was studied. Silver chloride was in each case precipitated almost quantitatively, but crude methyl 8-oxo-octadec-*cis*- and -*trans*-11-en-9-ynoate were difficult to purify. Distillation caused major losses of material but still did not effect complete purification, so the impure product was used directly in the next stage. The crude ester, however, showed the expected infrared characteristics for structure (I) and the en-yne-conjugated oxo-function was established by the ultraviolet max. at 268 mμ (ε 8000). Further, each stereoisomer gave 8-oxo-octadecanoic acid when hydrogenated.

In a trial run,* using a mixture of decenyne stereoisomers, an attempt was made to hydrolyse methyl 8-oxo-octadec-11-en-9-ynoate to the acid with aqueous-ethanolic potassium hydroxide before the borohydride reduction. The oily product, isolated after acidification, gave a strong red-violet ferric chloride reaction and its spectrum in neutral ethanol showed maxima at 278 and 282 mμ (ε 5700 for both), shifted by alkali to 298 and 300 mμ (ε 9000). This is characteristic of a 1 : 3-diketone and showed that under these conditions a net hydration of the acetylenic linkage had occurred. The infrared spectrum of the oil [bands at 1704 (CO_2H), 1653 (C=C), 1597 (enolised β-diketone), and 970 cm.$^{-1}$ (*trans*-CH=CH)] supports the assigned structure.

Reduction of crude methyl 8-oxo-octadec-*cis*-11- and -*trans*-11-en-9-ynoate with

* We thank Dr. A. G. Jacklin (Ph.D. Thesis, London, 1956) for this preliminary work which convinced us that synthesis of *cis*- and *trans*-8-hydroxyximenynic acid by the method reported here was feasible. These early results were communicated to Dr. B. C. L. Weedon who was independently contemplating a synthesis of 9 : 11-dioxononadecanoic acid, the ozonolysis product of sterculic acid, by a similar route. This has since been executed.[7]

[6] Allan and Whiting, *J.*, 1953, 3314.
[7] Narayanan and Weedon, *Chem. and Ind.*, 1957, 394.

potassium borohydride followed by acid, then alkaline, hydrolysis gave (±)-8-hydroxyoctadec-*cis*-11- and -*trans*-11-en-9-ynoic acid in 86 and 38% overall yield from 7-methoxycarbonylheptanoyl chloride. Attempted purification was incomplete, though chromatography on " neutral " alumina from benzene containing 0·5% of methanolic acetic acid gave fairly good results. The best technique proved to be distillation of the methyl esters. Both esters absorbed 3 mol. of hydrogen over a catalyst to give methyl (±)-8-hydroxyoctadecanoate and both gave *n*-heptanoic acid on ozonolysis. Crystalline *p*-phenylphenacyl esters were obtained from each geometrical isomer: data are summarised in Table 2.

TABLE 2. (±)-8-*Hydroxyoctadec*-cis-11- *and* -trans-11-*en*-9-*ynoic acid*.

	Methyl ester					
	B. p. at 10^{-3} mm.	n_D^{23}	Micro-hydrogn.	$\lambda_{max.}$ (mμ) [a]	$\nu_{max.}$ (cm.$^{-1}$) [a]	*p*-Phenylphenacyl ester, m. p.
cis-	152—156°	1·4806	3·00	228 (16,200)	735 (91·3)	55—55·5°
trans-	150—152	1·4842	2·95	229 (15,300)	955 (116)	67—68

[a] ε in parentheses.

At this stage it was hoped to compare the two synthetic (±)-8-hydroxyximenynic acids with natural (presumably optically active) acid by solution infrared techniques. Unfortunately we understand from Dr. Nunn that none of Dr. Ligthelm's unique specimen remains. Also no crystalline derivatives of the natural acid were reported, and we have been unable to obtain the original infrared trace. We can only say that the properties of our (±)-8-hydroxyoctadec-*trans*-11-en-9-ynoic acid agree with those of the natural acid in so far as the significant observations [1] from which Ligthelm deduced his structure can be duplicated on our synthetic *trans*-acid. Thus, apart from points already covered, alkaline isomerisation produces conjugated tetraene absorption in the ultraviolet, and boiling with lithium aluminium hydride in ether gives the diene-diol (VII) showing a strong conjugated *trans-trans* infrared absorption. The spectrum is readily distinguished from that of the *cis-trans*-diol similarly obtained from (±)-8-hydroxyoctadec-*cis*-11-en-9-ynoic acid. The (±)-*trans*-compound also forms a methyl ester acetate readily.

$$Me\cdot[CH_2]_5\cdot CH{=}CH\cdot CH{=}CH\cdot CH(OH)\cdot[CH_2]_7\cdot OH \quad \text{(VII)}$$

The availability of dec-*cis*-3-en-1-yne has enabled us to carry out a synthesis of *cis*-(unnatural)-ximenynic acid. The route follows that described in Part V (which led to the *trans*-acid), with certain modifications. Now that pimelic acid is easily made in high yield [8] from commercial pimelo-γ-dilactone,[9] we have reverted to Huber's route [10] to heptane-1 : 7-diol and hence 1-chloro-7-iodoheptane. Condensation of the latter with

TABLE 3. cis- *and* trans-*Ximenynic acid*.

	M. p.	Micro-hydrogn.	$\lambda_{max.}$ (mμ) [a]	CH=CH δ (cm.$^{-1}$)	*p*-Phenylphenacyl ester, m. p.
cis-	25·5—26·5°	2·95 H_2	227 (14,250)	737·5	42—43°
trans- [b]	39—40	2·95 H_2	228 (16,800)	952	61·5—62 [c]

[a] ε in parentheses. [b] Crombie and Jacklin (synthetic acid). [c] Ligthelm and Schwartz (natural acid).

sodiodecenyne proceeded smoothly only if freshly distilled liquid ammonia (from sodium) was used. Conversion of 17-chloroheptadec-*cis*-7-en-9-yne into the nitrile and then the corresponding acid caused little stereomutation, and traces of *trans*-contaminant were removed by repeated urea-complex formation. The *cis*-acid was isolated crystalline and its properties are compared with those of the *trans*-acid in Table 3.

[8] Gardner, Rand, and Haynes, *J. Amer. Chem. Soc.*, 1956, **78**, 3425.
[9] Cf. Hopff and Griesshaber, U.S.P. 2,302,321 (*Chem. Abs.*, 1943, **37**, 2020).
[10] Huber, *J. Amer. Chem. Soc.*, 1951, **73**, 2730.

XUM

Experimental

Hex-1-ynylsilver.—Silver nitrate (102·4 g.) was dissolved in water (500 ml.) containing methanol (300 ml.), and ammonia solution (*d* 0·880) added until the precipitate just redissolved. Hex-1-yne (24·8 g.) was added with cooling, and the mixture was shaken for 2 hr. The lilac-coloured solid was filtered off, washed until neutral, dissolved in carbon tetrachloride (300 ml.), and dried over calcium chloride.

Ethyl 6-Oxododec-7-ynoate.—5-Ethoxycarbonylpentanoyl chloride (38·1 g., 10% excess; b. p. 104—106°/5 mm., n_D^{22} 1·4481) was heated under reflux for 18 hr. with hexynylsilver in carbon tetrachloride (178 ml., above) and the precipitated silver chloride (23·5 g., 92%) was filtered off. The filtrate was washed with ammonia solution, 2N-hydrochloric acid, sodium hydrogen carbonate solution, and water. After drying ($MgSO_4$), evaporation, and distillation, *ethyl 6-oxododec-7-ynoate* (17·6 g., 36%), b. p. 129°/0·03 mm., n_D^{19} 1·4630, was isolated (Found: C, 69·8; H, 9·25. $C_{14}H_{22}O_3$ requires C, 70·55; H, 9·3%), $\lambda_{max.}$ 222 mμ (ε 9500), $\nu_{max.}$ 2225 (C≡C), 1740 (CO_2Et), and 1681 cm.$^{-1}$ (conjugated C=O). On hydrogenation in ethyl acetate over palladised charcoal, 2·16 mol. of hydrogen were absorbed. Working up and hydrolysis gave 6-oxododecanoic acid, m. p. 61·5—62° (Found: C, 67·5; H, 10·5. Calc. for $C_{12}H_{22}O_3$: C, 67·25; H, 10·35%). The semicarbazone had m. p. 132—132·5°. Keskin [11] gives m. p. 61·5° for 6-oxododecanoic acid and m. p. 132° for its semicarbazone.

When the oxo-acetylenic ester was treated with 10% ethanolic potassium hydroxide at room temperature for 24 hr., an acidic yellow oil was formed which gave a brown-red colour with ferric chloride and had infrared bands at 1712 (CO_2H) and 1585 cm.$^{-1}$ [C(OH)=CH·CO].

Methyl 6-Hydroxydodec-7-ynoate.—Potassium borohydride (4 g.) in water (45 ml.) was added to ethyl 6-oxododec-7-ynoate (6·8 g.) in methanol (360 ml.) and set aside at 0° for 20 hr. Potassium hydroxide (17·5 g.) was added and the mixture was refluxed for 5 hr. After evaporation of most of the methanol *in vacuo*, neutral material was removed with ether. The acid was then isolated, after acidification, as a yellow oil with infrared bands at 3311 (OH), 2244 (C≡C), and 1708 cm.$^{-1}$ (CO_2H). With diazomethane it gave *methyl 6-hydroxydodec-7-ynoate* (5·1 g., 67%), b. p. 112°/0·01 mm., n_D^{18} 1·4467 (Found: C, 68·55; H, 9·85. $C_{13}H_{22}O_3$ requires C, 69·0; H, 9·8%), $\nu_{max.}$ 3448 (OH), 2225 (C≡C), and 1739 cm.$^{-1}$ (CO_2Me).

*Dec-*cis*-3- and -*trans*-3-en-1-yne.*—Dec-1-yn-4-ol [4] (142·2 g.) was mixed with pyridine (74 ml.) and toluene-*p*-sulphonyl chloride (176 g.) and set aside for 48 hr. The product was poured into water and extracted with ether (4 × 100 ml.), and the united ethereal extracts were washed with 2N-hydrochloric acid, sodium hydrogen carbonate solution, and water. Evaporation of the dried ethereal solution gave the crude oily toluene-*p*-sulphonate (252 g., 89%) which was re-dissolved in ether (250 ml.) and added during 2 hr. to a solution of sodamide [from sodium (40 g.)] in liquid ammonia (3 l.). The solution was stirred overnight and ammonium chloride (200 g.) was added. The ammonia was allowed to evaporate and water (500 ml.) was added. The product was extracted with pentane (4 × 100 ml.), and the combined extracts were washed as above and dried ($MgSO_4$). Evaporation and distillation gave dec-3-en-1-yne (74 g., 67%), b. p. 74—78°/15 mm., n_D^{25} 1·4514. The infrared spectrum showed a band (CS_2 solution) at 954 cm.$^{-1}$ (ε 33·5) due to the out-of-plane *trans*-CH=CH vibration. Examination by vapour-phase chromatography showed two components to be present in roughly comparable quantity. Crombie and Jacklin [4] give b. p. 65°/10 mm., n_D^{20} 1·4500.

The mixture of geometrical isomers (144 g.) was fractionated under nitrogen in the presence of quinol (50 mg.), through a Stedman gauze-packed column provided with a heated jacket and automatic pressure-control. The reflux ratio was 48 : 1 and the operation was carried out continuously during 20 hr. Omitting fore-runnings and tailings the following fractions were taken at 51 mm.: (1) b. p. 89·8—90·0°, $n_D^{21·5}$ 1·4490 (15·4 g.); (2) b. p. 90°, $n_D^{21·5}$ 1·4500 (20·0 g.); (3) b. p. 90—91°, $n_D^{21·5}$ 1·4505 (16·7 g.); (4) b. p. 91—97·7°, $n_D^{21·5}$ 1·4536 (8·9 g.); (5) b. p. 97·7—99·2°, $n_D^{21·5}$ 1·4549 (12·9 g.); (6) b. p. 99·2—113·7, $n_D^{21·5}$ 1·4529 (2·1 g.). Fractions (1)—(3) are *dec-*cis*-3-en-1-yne*, fraction (2) being the purest (Found: C, 88·25; H, 11·95. $C_{10}H_{16}$ requires C, 88·2; H, 11·8%). There was no absorption near 955 cm.$^{-1}$. The hydrocarbon quickly became yellow at 20° and its refractive index changed: it was stored at low temperature in a sealed vessel under nitrogen. Fraction (5) is the *trans*-isomer (analysis below). It had an infrared band at 955 cm.$^{-1}$ (ε 115 in CS_2). This stereoisomer changed colour and refractive index only after several weeks.

[11] Keskin, *Rev. Fac. Sci. Univ. Istanbul*, 1952, **17**, *A*, 344.

XUM

Mercury Derivative of Dec-cis-3-*en*-1-*yne*.—Hydrocarbon from fraction (3) (1·36 g.) was dissolved in methanol (10 ml.) and shaken with a solution of potassium mercuric iodide (5 ml.) [made by adding a solution of potassium iodide (163 g.) and mercuric chloride (66 g.) in water (163 ml.) to 10% sodium hydroxide solution (125 ml.)]. The colourless oil (1 g.) which separated was extracted with light petroleum (b. p. 40—60°), washed, dried, concentrated *in vacuo*, and allowed to crystallise at low temperature. Two further crystallisations at low temperature from this solvent gave the cis-*mercury derivative* (cf. Table 1) [at 20° the oil ($n_D^{23\cdot5}$ 1·5467) became yellow] (Found: C, 50·9; H, 6·35. $C_{20}H_{36}Hg$ requires C, 50·4; H, 6·35%), $\nu_{max.}$ 2149 (C≡C), 1616 (conjugated C=C), and 737 cm.$^{-1}$ (*cis*-C=C: in CS_2, ε 12·0). There was no band at 3302 cm.$^{-1}$ (C≡CH).

Infrared spectra (cm.$^{-1}$ and ε) of dec-cis- *and dec*-trans-3-*en*-1-*yne*.*

cis		*cis*		*cis*		*trans*		*trans*	
3302	(64) [a]	1393 [c]		1006	(8) [b]	3291	(96) [a]	1263 [c]	
3022	(23) [b]	1380	(27) [b]	950	(7) [b]	3058	(218) [a]	1204	(18) [a]
2924	(195) [a]	1349 [c]		927 [c]		2915	(140) [a]	1114	(9) [b]
2907	(109) [a]	1318 [c]		905 [c]		2849	(21) [b]	1063	(9) [b]
2705 [c]		1298 [c]		888	(7) [b]	2116	(6) [b]	1029	(9) [b]
2110	(5) [b]	1271	(14) [b]	850 [c]		1629	(6) [b]	961	(119) [a]
1723	(13) [b]	1216	(29) [b]	817	(5) [b]	1461 [c]		882 [c]	
1695	(7) [b]	1115	(19) [b]	781 [c]		1440 [c]		865 [c]	
1618 [c]		1053	(8) [b]	742	(51) [a]	1378	(25) [b]	724	(9) [a]
1465 [c]		1043 inf. [c]		729 inf. [c]		1354	(2) [b]		
1444 inf. [c]						1303	(14) [b]		

* All frequencies measured on liquid film: ε in parentheses where measured.
[a] Apparent ε in 1% solution in CS_2. [b] Apparent ε in 3% solution in CS_2. [c] Band does not appear significantly in CS_2 solution.

The *cis*-mercury derivative was shaken with concentrated hydrochloric acid for 1 hr. at 20° and the liberated hydrocarbon was isolated with ether and distilled, to give pure dec-*cis*-3-en-1-yne (see Table 1; temp. coeff. of n −0·0004/°c) (Found: C, 88·0; H, 11·9%). The infrared spectrum (see below) was identical with that of fraction (2) above.

Mercury Derivative of Dec-trans-3-*en*-1-*yne*.—Hydrocarbon from fraction (5) (1·36 g.) gave, by the above procedure, a white solid (1·1 g.) which was crystallised three times from light petroleum (b. p. 40—60°), to give the trans-*mercury derivative* as leaflets (cf. Table 1) (Found: C, 50·8; H, 6·65%). The infrared spectrum was similar to that of the *cis*-derivative, but for a prominent band at 952 cm.$^{-1}$ (ε 31·0 in CS_2) and the absence of the prominent *cis*-band at 737 cm.$^{-1}$ (ε 12·0 for the *cis*-compound).

Regeneration of dec-*trans*-3-en-1-yne as above gave, after distillation, hydrocarbon (see Table 1; temp. coeff. of n −0·00038/°c) (Found: C, 88·0; H, 11·9%. Microhydrogenation 3·05H_2).

Silver Dec-cis-3-*en*-1-*yne*.—The hydrocarbon (6 g.) in methanol (30 ml.) was added dropwise to silver nitrate (15 g.) in water (50 ml.) to which sufficient ammonia solution (d 0·880) had been added just to redissolve the precipitate, and the whole was shaken for 15 min. at 10°. The oily precipitate of *silver dec*-cis-3-*en*-1-*yne* (solid below ~15°) was extracted with carbon tetrachloride (5 × 10 ml.), and the extract was washed with water until the washings were neutral. The extract was dried and filtered, and a portion (5 ml.) of the brown solution (58 ml.) gave silver chloride (0·426 g.) when treated with concentrated hydrochloric acid. This is equivalent to a yield of 77%.

7-*Methoxycarbonylheptanoyl Chloride*.—Dimethyl suberate (7·6 g., b. p. 78—82°/0·04 mm., n_D^{20} 1·4360), suberic acid (11·3 g.), di-*n*-butyl ether (4 ml.), and concentrated hydrochloric acid (1 ml.) were heated under reflux in an oil-bath at 170°. When homogeneous, the mixture was rapidly cooled and methanol (2·2 ml.) was added. The mixture was again heated in the oil-bath for 2 hr. After rapid cooling, methanol (0·7 ml.) was added and refluxing continued for a further 2 hr. On direct distillation methyl hydrogen suberate (7·7 g., 40%), b. p. 127—142°/0·06 mm., n_D^{17} 1·4460, was isolated. Bounds *et al.*[12] give b. p. 135—138°/0·12 mm., n_D^{17} 1·4461. The half-ester (9·3 g.) was heated under reflux for 5 hr. with thionyl chloride (6 ml.). Excess of reagent was removed at the pump and the product on distillation gave 7-methoxycarbonylheptanoyl chloride (8·5 g., 83%), b. p. 118—121°/3 mm., n_D^{20} 1·4495.

[12] Bounds, Linstead, and Weedon, *J.*, 1954, 448.

XUM

Methyl 8-*Oxo-octadec*-cis-11-*en*-9-*ynoate*.—A solution of silver dec-*cis*-3-en-1-yne in carbon tetrachloride (53 ml.; see above: it represents a 39% excess) was heated under reflux in nitrogen for 24 hr. with 7-methoxycarbonylheptanoyl chloride (5·08 g.). The precipitated silver chloride (4·2 g., 99%) was filtered off through kieselguhr, and the filtrate was shaken with 0·1N-ammonia and 0·1N-hydrochloric acid and then washed with water until neutral. After drying, the solution was evaporated and distilled to give crude methyl 8-oxo-octadec-*cis*-11-en-9-ynoate (2·2 g., 29%), b. p. 152°/10^{-3} mm., $n_D^{21·5}$ 1·4788. There was an ultraviolet maximum at 268 mμ (ε 8200), the curve being broad and rather flat between 266 and 272 mμ. In the infrared there were bands at 2193 (conjugated C≡C), 1739 (CO_2Me), 1674 (conjugated C=O), 1610 and 740 cm.$^{-1}$ (conjugated *cis*-CH=CH). There was no band at 950 cm.$^{-1}$. Other runs gave yields of 14—22%, the distilled product being brown and of somewhat variable refractive index. For preparative work undistilled ester, $n_D^{22·5}$ 1·4894, obtained in 79% yield, was used [$\lambda_{max.}$ 266 mμ (ε 7200)]. Its infrared spectrum differed only from that of distilled material in bands at 1712 (saturated acid or ester impurity) and at 1567 cm.$^{-1}$ (slight, β-diketone)

An ethanolic solution (0·03%) of the ester, on treatment with aqueous alkali, exhibited a new maximum after 24 hr. at 293 mμ (ε 10,300): this was displaced to 259 mμ (ε 11,500) after acidification. Methyl 8-oxo-octadec-*cis*-11-en-9-ynoate (50 mg.) was dissolved in 10% ethanolic alkali (2 ml.) and after 24 hr. the acidic product was isolated as a brown oil which showed a strong ferric chloride reaction and bands at 1706 (CO_2H) and 1586 cm.$^{-1}$ [CH(OH)=CH·CO]. Methyl 8-oxo-octadec-*cis*-11-en-9-ynoate (0·182 g.) was hydrogenated in methanol (15 ml.) over palladised charcoal and absorbed 95·5% of the expected volume of hydrogen for saturation of the en-yne system. After filtration, the product was hydrolysed with sodium hydroxide to 8-oxostearic acid, m. p. 83·5—84° [from chloroform–light petroleum (b. p. 40—60°)] (Found: C, 72·15; H, 11·35. Calc. for $C_{18}H_{34}O_3$: C, 72·45; H, 11·5%). The m. p. was undepressed on admixture with a specimen of the authentic keto-acid (m. p. 83—83·5°).

8-*Hydroxyoctadec*-cis-11-*en*-9-*ynoic Acid*.—Undistilled methyl 8-oxo-octadec-*cis*-11-en-9-ynoate (4·42 g.) in methanol (300 ml.) was treated with potassium borohydride (2 g.) in water (20 ml.) at 5°. After 2 days the mixture was acidified with concentrated hydrochloric acid, the methanol was removed *in vacuo*, and the product was hydrolysed by refluxing it for 1 hr. with sodium hydroxide (1 g.). The solution was diluted with brine (100 ml.), neutral material was removed by extraction with ether, and, after acidification, the acidic product was collected with ether. The ethereal solution was washed, dried ($MgSO_4$), and evaporated to give an oil (3·67 g., 86%) having infrared bands at 3280 (OH), 2224 (C≡C), 1713 (CO_2H), 1597 (conjugated C=C) and 737·5 cm.$^{-1}$ (*cis*-CH=CH). Attempted urea-complex formation, low-temperature crystallisation, purification through the lead or benzylamine salts, and reversed-phase partition chromatography all failed to effect complete purification. Best results were obtained by chromatography on neutral alumina from benzene solution, and elution with 0·5% methanolic acetic acid. The product was then obtained as a pale-yellow oil, $n_D^{20·5}$ 1·4801, $\lambda_{max.}$ 226·6 mμ (ε 13,520) (Found: C, 72·45; H, 10·35. Calc. for $C_{18}H_{30}O_3$: C, 73·45; H, 10·25%. Microhydrogenation 2·71 H_2). There was no infrared band near 955 cm.$^{-1}$: the *cis*-band at 735·3 cm.$^{-1}$ had ε 56·5 in CS_2. For further purification the acid (1 g.) was converted by diazomethane into the *methyl ester* which after two distillations had b. p. 152—156°/10^{-3} mm., n_D^{23} 1·4806 (0·625 g.) (Found: C, 73·75; H, 10·35. $C_{19}H_{32}O_3$ requires C, 73·95; H, 10·45%. Microhydrogenation 3·0 H_2), $\lambda_{max.}$ 228 mμ (ε 16,200), $\nu_{max.}$ (liquid film) 3390 (OH), 2259 (C≡C), 1743 (CO_2Me), 1608 (conjugated C=C) and 735 cm.$^{-1}$ (conjugated *cis*-CH=CH) (in CS_2 the last band had ε 91·3). Hydrogenation of the methyl ester gave methyl 8-hydroxyoctadecanoate, m. p. 54·5—55·5° (Found: C, 72·65; H, 12·7. $C_{19}H_{38}O_3$ requires C, 72·55; H, 12·2%). p-*Phenylphenacyl* 8-*hydroxyoctadec*-cis-11-*en*-9-*ynoate* was purified chromatographically and had m. p. 55—55·5° (Found: C, 78·8; H, 8·3. $C_{32}H_{40}O_4$ requires C, 78·65; H, 8·25%).

Ozonolysis of Methyl 8-*Hydroxyoctadec*-cis-11-*en*-9-*ynoate*.—The methyl ester (0·107 g.) in glacial acetic acid (4 ml.) and ethyl acetate (2 ml.) was ozonised at 0°. The solvent was removed at the pump, hydrogen peroxide (100-vol.; 1 ml.) and acetic acid (4 ml.) were added, and the mixture was set aside for three days. The solvents were removed *in vacuo* and the acidic residue was esterified with diazomethane. Methyl *n*-heptanoate was identified by a gas–liquid phase chromatogram and mixed chromatogram.

Reduction of 8-*Hydroxyoctadec*-cis-11-*en*-9-*ynoic Acid with Lithium Aluminium Hydride*.—The crude acid (0·758 g.) in ether (5 ml.) was added to a suspension of lithium aluminium

hydride (0·61 g.) in ether (12 ml.) and heated under reflux for 1 hr. After cooling, ethyl acetate (10 ml.) was added and then 5% sulphuric acid (10 ml.). Extraction with ether, followed by distillation, gave octadeca-*trans*-9 : *cis*-11-diene-1 : 8-diol (0·423 g.), b. p. 166°/10^{-3} mm., $n_D^{20\cdot5}$ 1·4892. Analysis indicates that it was not quite pure [Found: C, 75·7; H, 12·0. Calc. for $C_{18}H_{34}O_2$: C, 76·55; H, 12·15%. Microhydrogenation 2·4 H_2 (saturation of two double bonds and perhaps some allylic cleavage of the 8-hydroxyl)], $\lambda_{max.}$ 229·5 mμ (ε 19,780), $\nu_{max.}$ 3355 (OH), 1663 and 1622 (conjugated diene), 986 and 944 (conjugated *cis-trans*-diene), 736 cm.$^{-1}$ (*cis*-C=C). The impurity was revealed by traces of absorption at 2259 (C≡C) and 1744 (ester) cm.$^{-1}$.

Silver Dec-trans-3-*en*-1-*yne*.—This was prepared from hydrocarbon (6 g.) as described for the *cis*-compound, with shaking for 2 hr. during which the silver derivative was precipitated as a grey sticky solid. It was extracted with carbon tetrachloride; an aliquot part (2 ml.) of the solution (65·5 ml.) yielded 0·132 g. of silver chloride, equivalent to a yield of 68·5%. Another run gave 61·5% yield.

Methyl 8-*Oxo-octadec*-trans-11-*en*-9-*ynoate*.—A solution of the silver salt of dec-*trans*-3-en-1-yne in carbon tetrachloride (63·5 ml.; see above: it represents a 26% excess) was heated under reflux and in nitrogen for 24 hr. with 7-methoxycarbonylheptanoyl chloride (4·7 g.). Silver chloride (3·7 g., 94%) was precipitated and the solution was worked up as in the case of the *cis*-stereoisomer to give crude methyl 8-oxo-octadec-*trans*-11-en-9-ynoate (7·08 g.). The ultraviolet max. was at 264·5 mμ (ε 8000), raised after chromatography on " neutral " alumina (from benzene) to ε 10,300. Infrared spectral max. were at 2186 (C≡C), 1740 (CO_2Me), 1672 (conjugated C=O), 1625 (C=C), and 959 cm.$^{-1}$ (*trans*-CH=CH). An ethanolic solution of the ester (0·06%), on treatment with aqueous alkali showed, after 24 hr., an ultraviolet max. at 286—290 mμ (ε 7200), displaced on acidification to 263 mμ (ε 6750). Isolation of the product in a larger scale experiment gave a product having bands at 1712 (CO_2H), 1595 [C(OH)=CH·CO], and 953 cm.$^{-1}$ (*trans*-CH=CH). Hydrogenation of the crude ester was possible only after it had been shaken with Raney nickel for 12 hr. Using palladium–strontium carbonate and hydrolysing the product gave 8-oxo-octadecanoic acid, m. p. and mixed m. p. 83° (Found: C, 72·9; H, 11·55%). Crude, undistilled, oxo-ester was used below.

8-*Hydroxyoctadec*-trans-11-*en*-9-*ynoic Acid*.—The oxo-ester (3·55 g.) in methanol (200 ml.) was treated with potassium borohydride (4 g.) in water (15 ml.) at 5°. After being set aside for 3 days the solution was acidified and the solvents were removed *in vacuo*. The residue was hydrolysed (45 min.) with sodium hydroxide (0·6 g.) in methanol (20 ml.), and the crude 8-hydroxyoctadec-*trans*-11-en-9-ynoic acid (1·29 g.) was isolated as a brown semi-solid, m. p. 29—34°, $\lambda_{max.}$ 228·6 mμ (ε 13,500). The acid (0·726 g.) was esterified with diazomethane, to give the pure *methyl ester* (0·266 g.), b. p. 150—152°/10^{-3} mm., n_D^{21} 1·4850 (Found: C, 73·8; H, 10·4. $C_{19}H_{32}O_3$ requires C, 73·95; H, 10·45%. Microhydrogenation 2·95 H_2), $\lambda_{max.}$ 229 mμ (ε 15,320). In the infrared there were bands at $\nu_{max.}$ 3429 (OH), 2225 (C≡C), 1755 (CO_2Me), 1601 (C=C), and 955 cm.$^{-1}$ (*trans*-CH=CH) [the ε value (CS_2) for the last band was 116]. On hydrogenation over palladised charcoal, the ester yielded methyl 8-hydroxyoctadecanoate, m. p. 54·5—55·5° (Found: C, 72·95; H, 12·25. Calc. for $C_{19}H_{38}O_3$: C, 72·55; H, 12·2%). When heated with acetic anhydride (15 ml.) and anhydrous sodium acetate (1 g.) for 3 hr., followed by isolation and then treatment with diazomethane, methyl 8-hydroxyoctadec-*trans*-11-en-9-ynoate (100 mg.) gave *methyl* 8-*acetoxyoctadec*-trans-11-*en*-9-*ynoate* (80 mg.), b. p. 130°/10^{-4} mm., $n_D^{23\cdot5}$ 1·4726 (Found: C, 72·4; H, 9·8. $C_{21}H_{34}O_4$ requires C, 71·95; H, 9·75%. Microhydrogenation 2·95 H_2), $\lambda_{max.}$ 228·5 mμ (ε 15,360), $\nu_{max.}$ 2235 (C≡C), 1743 (ester), 1652 (C=C), and 960 cm.$^{-1}$ (*trans*-CH=CH). p-*Phenylphenacyl* 8-*hydroxyoctadec*-trans-11-*en*-9-*ynoate* had m. p. 67—68° after purification by chromatography (Found: C, 78·45; H, 8·5%).

Reduction of Methyl 8-*Hydroxyoctadec*-trans-11-*en*-9-*ynoate with Lithium Aluminium Hydride*.—The ester (0·209 g.) in ether (5 ml.) was treated with a suspension of lithium aluminium hydride (0·5 g.) in ether (10 ml.), and the mixture was heated under reflux (2 hr.) and then worked up as described above. Octadeca-*trans*-9 : *trans*-11-diene-1 : 8-diol (0·115 g., undistilled) was isolated but did not crystallise; it had $\lambda_{max.}$ 231·2 mμ (ε 15,200), and $\nu_{max.}$ at 3367 (OH), 1661 (C=C), and 988 cm.$^{-1}$ (*trans-trans*-diene).

Ozonolysis of Methyl 8-*Hydroxyoctadec*-trans-11-*en*-9-*ynoate*.—This was effected on the ester (46 mg.) according to the procedure described for the *cis*-stereoisomer, and methyl-*n*-heptanoate identified by gas–liquid chromatography.

Alkaline Isomerisation of 8-*Hydroxyoctadec*-trans-11-*en*-9-*ynoic Acid*.—The acid (1·98 mg.)

XUM

in a 6% solution of potassium hydroxide in ethylene glycol (2 ml.) was heated to 180° for 35 min., cooled rapidly, and diluted with ethanol to 25 ml. Spectroscopic examination against a blank determination carried out at the same time showed reduction of the intensity of the band at 229·8 mμ (ε 13,000) and the appearance of new bands at 263 (ε 3440), 298 (1210), and 313 mμ (ε 970, inflexion).

Heptane-1 : 7-*diol*.—Pimelic acid was prepared from commerical[9] pimelo-γ-dilactone in 98·5% yield by Huang-Minlon reduction,[8] and converted into the diethyl ester (b. p. 114—120°/1 mm., n_D^{22} 1·4291) by refluxing it for 12 hr. with ethanol, benzene, and sulphuric acid (yield 85%). The ester was reduced by Huber's method,[10] but by paying greater attention to the extraction procedure (adding sodium carbonate and evaporating the liquors after as much diol as possible had been removed in ether, and then re-extracting), the yield of heptane-1 : 7-diol, m. p. 20°, b. p. 139—140°/~2 mm., $n_D^{24·5}$ 1·4528, was increased to 71%.

1-*Chloro*-7-*iodoheptane*.—By the procedures described in Part V, heptane-1 : 7-diol gave 1 : 7-dichloroheptane (70%) which in turn gave 1-chloro-7-iodoheptane, b. p. 80—90°/0·3 mm., n_D^{20} 1·5206, in 41·5% yield.

1-*Chloroheptadec*-cis-10-*en*-8-*yne*.—Dec-*cis*-3-en-1-yne (9·08 g.) was added to a stirred solution of sodamide prepared from freshly distilled (from sodium) liquid ammonia (200 ml.), sodium (1·5 g.), and ferric nitrate (50 mg.) and contained in a strip-silvered vacuum-flask. After 3½ hr., a clear yellow solution was obtained and 1-chloro-7-iodoheptane (17·5 g.) was added during 30 min. The mixture was stirred for 18 hr., ammonium chloride (10 g.) added, and the ammonia allowed to evaporate. Water (50 ml.) was added and the product extracted with light petroleum (b. p. 40—60°) (5 × 10 ml.). The extracts were washed with 2N-hydrochloric acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and distilled, to give 1-*chloroheptadec*-cis-10-*en*-8-*yne* (9·0 g., 50%), b. p. 128—132°/10^{-3} mm., n_D^{22} 1·4812 (Found: C, 75·25; H, 10·9. $C_{17}H_{29}Cl$ requires C, 75·95; H, 10·85%), $\lambda_{max.}$ 226·5 mμ (ε 14,820), and $\nu_{max.}$ 2207 (C≡C), 1611 (C=C), and 734 (*cis*-CH=CH) cm.$^{-1}$. The band at 954 cm.$^{-1}$ (*trans*-CH=CH conjugated with an acetylenic linkage) characteristic of the *trans*-isomer (Part V) was absent.

Another run gave a yield of 26·5% but two using undistilled liquid ammonia gave yields of only 8·5% and 5%.

Octadec-cis-11-*en*-9-*ynoic Acid*.—1-Chloroheptadec-*cis*-10-en-8-yne (4·1 g.) was heated under reflux for 16 hr. with sodium iodide (5 g.) in acetone. After evaporation of the acetone the residue was extracted with light petroleum (b. p. 40—60°), and the extracts were washed with sodium thiosulphate solution. Drying ($MgSO_4$) and evaporation gave crude iodo-compound showing no infrared band near 954 cm.$^{-1}$.

The crude iodide was heated under reflux with potassium cyanide (5 g.) in ethanol (40 ml.) and water (10 ml.) for 18 hr. Most of the ethanol was evaporated *in vacuo* and the residual solution was extracted with ether. After drying and evaporation these extracts gave crude nitrile (4·0 g.) showing infrared bands at 2200 (C≡C) and 2240 (·C≡N) cm.$^{-1}$ but none near 954 cm.$^{-1}$. The nitrile was heated under reflux for 48 hr. with potassium hydroxide (5 g.) in 80% aqueous ethanol (50 ml.): ammonia had by then ceased to be evolved. Isolation of the crude acid in the usual way yielded a yellow oil (2·72 g.) which was dissolved in hot methanol (20 ml.) saturated with urea. The mixture was cooled to 0° and the precipitate removed. The filtrate was re-saturated with urea, and the cooling and filtration were repeated. The process was repeated twice more. [Dissolution of these urea precipitates in water afforded 56 mg. of very crude *trans*-ximenynic acid (infrared spectrum).] The final filtrate was poured into water, and the purified acid isolated by ether-extraction as a yellow oil (1·84 g.). On dissolution in light petroleum (b. p. 40—60°) and storage at 0°, an impurity (63 mg.) of m. p. 98—106° was deposited; it was filtered off. The acid in the filtrate was recovered and crystallised five times at low temperature from a mixture of light petroleum (b. p. 40—60°) and methylene chloride. *Octadec*-cis-11-*en*-9-*ynoic acid* was obtained having m. p. 25·5—26·5°, $n_D^{21·5}$ 1·4843 (supercooled) (Found: C, 77·4; H, 10·8. $C_{18}H_{30}O_2$ requires C, 77·65; H, 10·85%. Microhydrogenation 2·95 H_2), $\lambda_{max.}$ 226·9 mμ (ε 14,250), $\nu_{max.}$ 2225 (C≡C), 1709 and 937 (CO_2H), 1617 (C=C), and 737·5 (*cis*-CH=CH) cm.$^{-1}$. There was no band at 952 cm.$^{-1}$ as in the spectrum of *trans*-ximenynic acid. The p-*phenylphenacyl ester*, crystallised from light petroleum (b. p. 60—80°), had m. p. 42—43° (Found: C, 81·55; H, 8·45. $C_{32}H_{40}O_3$ requires C, 81·3; H, 8·53%). The *methyl ester* had b. p. 130—132°/6 × 10^{-4} mm., $n_D^{24·5}$ 1·4690 (Found: C, 77·5; H, 11·2. $C_{19}H_{32}O_2$ requires C, 78·0; H, 11·0%), $\lambda_{max.}$ 226·8 mμ (ε 13,920), $\nu_{max.}$ 2225 (C≡C), 1740 (CO_2Me), 1620, and 737·5 (*cis*-CH=CH) cm.$^{-1}$, but no maximum near 952 cm^{-1}. On ozonolysis under the conditions

described above, followed by conversion of the products into their methyl esters, *cis*-ximenynic acid (51 mg.) yielded methyl *n*-heptanoate and dimethyl azelaate, identified by gas–liquid chromatography.

We thank Dr. J. R. Nunn for a specimen of 8-oxo-octadecanoic acid. One of us (B. P. G.) acknowledges with gratitude a State Scholarship and a grant from the Chemical Society for the purchase of certain chemicals.

DEPARTMENT OF CHEMISTRY,
IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W.7.

[*Received, July 14th*, 1958.]

---

898. *The Relationship between the Excess Heat and Volume of Mixing.*

By A. R. MATHIESON.

Equations are derived for binary liquid mixtures relating the heat of mixing to the excess volume and compressibility, and the excess compressibility to the excess volume and vapour pressure. The equations are applied to the systems *cyclo*hexane–carbon tetrachloride, benzene–toluene, benzene–carbon tetrachloride, benzene–*cyclo*hexane and ethanol–water, and it is shown that for the non-polar mixtures it is possible to calculate the heat of mixing from density measurements and the compressibilities of the pure components where the excess vapour pressure is always very small. For systems with larger excess vapour pressures these need to be known also. The theoretical significance of the equations is discussed, and comparison is made with recent theories of non-electrolyte solutions.

THE variation of the excess thermodynamic functions of mixing with concentration for many binary liquid mixtures can be represented by equations of the same form in mole fraction (x) or volume fraction (ϕ). In particular, the excess heat (ΔH_m) and excess volume (ΔV_m) at constant pressure and temperature can frequently be expressed by equations of the form

$$\Delta H_m = x_1 x_2[A + B(x_1 - x_2) + C(x_1 - x_2)^2] \quad . \quad . \quad . \quad . \quad (1)$$

$$\Delta V_m = x_1 x_2[D + E(x_1 - x_2) + F(x_1 - x_2)^2] \quad . \quad . \quad . \quad . \quad (2)$$

where x_1, x_2 are the mole fractions of the two components and A, B, C, D, E, F are constants. Equations of the same form hold for ϕ. This has been demonstrated for the ten binary mixtures formed from benzene, toluene, *n*-hexane, *n*-heptane, and *cyclo*hexane,[1,2] and for binary mixtures of benzyl acetate with chloroform, *m*-cresol, dioxan, and aniline.[3] In other cases where investigators have expressed their results differently, (1) and (2) often describe the results as well. For benzyl acetate–aniline it is striking how similar is the form of the variation of ΔH_m and ΔV_m with x, each showing a maximum and a minimum at almost the same values of x[3]. The variations with x of ΔH_m and ΔV_m seem to be related, and Newitt and Weale,[4] who studied mixtures containing hexane, heptane, and octane, and mixtures of alcohols, suggested that a relationship must exist between the excess heat of mixing, the molar volume, and the compressibility. Such a relationship might be useful if it enabled heats of mixing, which are tedious to measure, to be calculated from simpler measurements such as that of density, and would have important theoretical implications.

Theoretical.—Equations relating the excess heat and volume of mixing. A thermodynamic

[1] Brown, Mathieson, and Thynne, *J.*, 1955, 4141.
[2] Mathieson and Thynne, *J.*, 1956, 3708.
[3] Moore and Styan, *Trans. Faraday Soc.*, 1956, **52**, 1556.
[4] Newitt and Weale, *J.*, 1951, 3092.

relationship can be obtained giving the differential of the excess heat content with concentration in terms of the excess compressibility, the excess volume and its differentials with temperature and concentration, and a constant volume term.

The heat content is a function of the four variables $H = F(P, V, T, x)$ and the pressure of the three

$$P = G(V, T, x) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Partial differentiation gives dH in terms of the two sets of variables V, T, x and P, V, T as

$$dH = \left(\frac{\partial H}{\partial V}\right)_{T,x} dV + \left(\frac{\partial H}{\partial T}\right)_{V,x} dT + \left(\frac{\partial H}{\partial x}\right)_{V,T} dx$$

$$= \left(\frac{\partial H}{\partial V}\right)_{P,T} dV + \left(\frac{\partial H}{\partial T}\right)_{P,V} dT + \left(\frac{\partial H}{\partial P}\right)_{V,T} dP$$

At constant T, then,

$$\left(\frac{\partial H}{\partial V}\right)_{T,x} = \left(\frac{\partial H}{\partial V}\right)_{P,T} + \left(\frac{\partial H}{\partial P}\right)_{V,T}\left(\frac{\partial P}{\partial V}\right)_{T} - \left(\frac{\partial H}{\partial x}\right)_{V,T}\left(\frac{\partial x}{\partial V}\right)_{T} \quad . \quad . \quad (4)$$

Partial differentiation also gives

$$dP = \left(\frac{\partial P}{\partial V}\right)_{T,x} dV + \left(\frac{\partial P}{\partial T}\right)_{V,x} dT + \left(\frac{\partial P}{\partial x}\right)_{V,T} dx$$

which at constant T yields

$$\left(\frac{\partial P}{\partial V}\right)_{T} = \left(\frac{\partial P}{\partial V}\right)_{T,x} + \left(\frac{\partial P}{\partial x}\right)_{V,T}\left(\frac{\partial x}{\partial V}\right)_{T} \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Combining (5) with (4), we have

$$\left(\frac{\partial H}{\partial V}\right)_{T,x} = \left(\frac{\partial H}{\partial V}\right)_{P,T} + \left(\frac{\partial H}{\partial P}\right)_{V,T}\left(\frac{\partial P}{\partial V}\right)_{T,x} + \left(\frac{\partial x}{\partial V}\right)_{T}\left[\left(\frac{\partial H}{\partial P}\right)_{V,T}\left(\frac{\partial P}{\partial x}\right)_{V,T} - \left(\frac{\partial H}{\partial x}\right)_{V,T}\right] \quad . \quad (6)$$

Since the following hold for these functions

$$\left(\frac{\partial H}{\partial x}\right)_{V,T} = \left(\frac{\partial H}{\partial P}\right)_{V,T}\left(\frac{\partial P}{\partial x}\right)_{V,T} \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$$\left(\frac{\partial H}{\partial V}\right)_{T,x} = \left(\frac{\partial H}{\partial P}\right)_{T,x}\left(\frac{\partial P}{\partial V}\right)_{T,x}; \quad \left(\frac{\partial H}{\partial V}\right)_{P,T} = \left(\frac{\partial H}{\partial x}\right)_{P,T}\left(\frac{\partial x}{\partial V}\right)_{P,T} \quad . \quad . \quad (8)$$

and (7) shows that the last term in (6) is zero, combination of (7) and (8) with (6) gives

$$\left(\frac{\partial H}{\partial P}\right)_{T,x}\left(\frac{\partial P}{\partial V}\right)_{T,x} = \left(\frac{\partial H}{\partial x}\right)_{P,T}\left(\frac{\partial x}{\partial V}\right)_{P,T} + \left(\frac{\partial H}{\partial P}\right)_{V,T}\left(\frac{\partial P}{\partial V}\right)_{T,x}$$

Rearranging, we have

$$\left(\frac{\partial H}{\partial x}\right)_{P,T}\left(\frac{\partial x}{\partial V}\right)_{P,T} = \left(\frac{\partial P}{\partial V}\right)_{T,x}\left[\left(\frac{\partial H}{\partial P}\right)_{T,x} - \left(\frac{\partial H}{\partial P}\right)_{V,T}\right] \quad . \quad . \quad . \quad (9)$$

For these functions also,

$$\left(\frac{\partial H}{\partial P}\right)_{V,T} = \left(\frac{\partial H}{\partial x}\right)_{V,T}\left(\frac{\partial x}{\partial P}\right)_{V,T}; \quad \left(\frac{\partial x}{\partial P}\right)_{V,T} = -\left(\frac{\partial V}{\partial P}\right)_{T,x}\left(\frac{\partial x}{\partial V}\right)_{P,T} \quad . \quad . \quad (10)$$

and combination with (9) gives

$$\left(\frac{\partial H}{\partial x}\right)_{P,T} = \left(\frac{\partial V}{\partial x}\right)_{P,T}\left(\frac{\partial P}{\partial V}\right)_{T,x}\left(\frac{\partial H}{\partial P}\right)_{T,x} + \left(\frac{\partial H}{\partial x}\right)_{V,T} \quad . \quad . \quad . \quad . \quad (11)$$

Equation (11) can be applied to the process of mixing the two components, for which $\Delta H_m = H_m - H_0$ and $\Delta V_m = V_m - V_0$, where H_m, V_m are the heat content and molar volume of the mixture, and H_0, V_0 are the corresponding additive functions for the separated components. Then,

$$\left(\frac{\partial \Delta H_m}{\partial x}\right)_{P,T} = \left(\frac{\partial \Delta V_m}{\partial x}\right)_{P,T}\left(\frac{\partial P}{\partial \Delta V_m}\right)_{T,x}\left(\frac{\partial \Delta H_m}{\partial P}\right)_{T,x} + \left(\frac{\partial \Delta H_m}{\partial x}\right)_{\Delta V_m,T} \quad . \quad (12)$$

On introduction of

$$\left(\frac{\partial \Delta H_m}{\partial P}\right)_{T,x} = \Delta V_m - T\left(\frac{\partial \Delta V_m}{\partial T}\right)_{P,x} \quad . \quad . \quad . \quad . \quad . \quad (13)$$

and

$$\left(\frac{\partial \Delta V_m}{\partial P}\right)_{T,x} = (\beta_0 V_0 - \beta_m V_m)_{T,x} \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

where β_m, β_0 are respectively the isothermal compressibilities of the mixture and the corresponding additive function for the separated components, equation (12) becomes

$$\left(\frac{\partial \Delta H_m}{\partial x}\right)_{P,T} = \left(\frac{\partial \Delta V_m}{\partial x}\right)_{P,T}\left(\frac{1}{\beta_0 V_0 - \beta_m V_m}\right)_{T,x}\left[\Delta V_m - T\left(\frac{\partial \Delta V_m}{\partial T}\right)_{P,x}\right] + \left(\frac{\partial \Delta H_m}{\partial x}\right)_{\Delta V_m,T} \quad . \quad . \quad . \quad . \quad (15a)$$

The corresponding equation for volume fraction is

$$\left(\frac{\partial \Delta H_m}{\partial \phi}\right)_{P,T} = \left(\frac{\partial \Delta v_m}{\partial \phi}\right)_{P,T}\left(\frac{1}{100(\beta_0 V_0 - \beta_m V_m)}\right)_{T,\phi}\left[\Delta V_m - T\left(\frac{\partial \Delta V_m}{\partial T}\right)_{P,\phi}\right] + \left(\frac{\partial \Delta H_m}{\partial \phi}\right)_{\Delta V_m,T} \quad . \quad . \quad . \quad . \quad (15b)$$

where $\Delta v_m = 100\Delta V_m/V_0$ and ΔH_m is expressed per ml. instead of per mole as in equation (15*a*). Application of these equations to the calculation of ΔH_m requires knowledge of the density over a small range of temperature and of the compressibility together with some information regarding the quantity $(\partial \Delta H_m/\partial x)_{\Delta V_m,T}$. There is reason to believe that this term is zero or negligible, at least for non-polar mixtures. The regular-solution approximation as applied by Scott [5] makes ΔH_m constant at constant ΔV_m, and the smoothed-potential cell model of Prigogine and Mathot [6] leads to the conclusion that ΔV_m is proportional to the other excess functions for non-polar mixtures. This is elaborated in the Discussion where the equations presented here are compared with several theories of mixtures. Experimental confirmation that $(\partial \Delta H_m/\partial x)_{\Delta V_m,T}$ is zero or negligible has been obtained for the non-polar mixtures examined.

Equations relating excess compressibility and vapour pressure. Knowledge of β_m is required for the practical application of equations (15) to the calculation of heats of mixing. For systems which depart sufficiently from ideality for the approximation $\beta_m = \beta_0$ to be invalid, β_m can be calculated from the vapour pressure.

Let $\Delta p = p_m - p_0$ where p_m, p_0 are the vapour pressure of the mixture and the additive vapour pressure of the separated components (the "ideal" vapour pressure). Then $\Delta p = f''(P, \Delta V_m, T, x)$ and analogous treatment to that for ΔH_m leads to

$$\left(\frac{\partial \Delta p}{\partial x}\right)_{P,T} = \left(\frac{\partial \Delta V_m}{\partial x}\right)_{P,T}\left(\frac{\partial P}{\partial \Delta V_m}\right)_{T,x}\left(\frac{\partial \Delta p}{\partial P}\right)_{T,x} + \left(\frac{\partial \Delta p}{\partial x}\right)_{\Delta V_m,T} \quad . \quad . \quad (16)$$

$(\partial \Delta p/\partial x)_{\Delta V_m,T}$ may be zero or negligible for non-polar mixtures, which is virtually the same assumption as for $(\partial \Delta H_m/\partial x)_{\Delta V_m,T}$. It holds when ΔF_m (the excess free energy) is proportional to ΔV_m, which is predicted theoretically for non-polar mixtures.[5,6] This assumption agrees with experiment for two non-polar mixtures.

[5] Scott, *Discuss. Faraday Soc.*, 1953, **15**, 44.
[6] Prigogine and Mathot, *J. Chem. Phys.*, 1952, **20**, 49.

XUM

If we put

$$\left(\frac{\partial \Delta p}{\partial P}\right)_{T,x} = \frac{d}{d_m - d} - \frac{d}{d_0 - d} \quad \ldots \ldots \quad (17)$$

where d_m, d_0, d are the densities of the mixture, the additive density of the separated components, and the density of the vapour, assumed ideal, (16) becomes, with (14), for non-polar mixtures,

$$\beta_0 V_0 - \beta_m V_m = \left(\frac{\partial \Delta V_m}{\partial \Delta p}\right)_{P,T}\left[\frac{d}{d_m - d} - \frac{d}{d_0 - d}\right] \quad \ldots \ldots \quad (18)$$

Equation (18) permits the calculation of β_m from the densities, and the compressibilities of the pure components.

Application of the Equations to Specific Mixtures.—Equations (15) and (18) were used to calculate the heat of mixing for different types of binary mixture and the results were compared with experimental values. Three groups of mixtures were considered and representatives taken from each. (1) Mixtures showing very small departures from ideality, for which $\beta_m = \beta_0$ (*cyclo*hexane–carbon tetrachloride, benzene–toluene). (2) Mixtures showing larger departures from ideality, for which $\beta_m \neq \beta_0$ (benzene–carbon tetrachloride, benzene–*cyclo*hexane). (3) Polar mixtures, for which $\beta_m \neq \beta_0$ and $(\partial \Delta H_m/\partial x)_{\Delta V_m, T}$ is probably not zero (ethanol–water).

For group (1), ΔH_m can be calculated from (15) with $\beta_m = \beta_0$, and for group (2), from (15) and (18). This test of the equations is necessary to show whether normal experimental measurements of density and compressibility are sufficiently accurate for a useful calculation, and to show empirically that $(\partial \Delta H_m/\partial x)_{\Delta V_m, T}$ and $(\partial \Delta p/\partial x)_{\Delta V_m, T}$ are negligible.

cyclo*Hexane–carbon tetrachloride.*' For the heat of mixing at 20° Scatchard, Ticknor, Goates, and McCartney [7] give

$$\Delta H_m = \phi_1 \phi_2 V_0[1{\cdot}49 + 0{\cdot}49(\phi_1 - \phi_2)^2]$$

where ϕ_1, ϕ_2 are the volume fractions of carbon tetrachloride and *cyclo*hexane, respectively, and ΔH_m is in cal./mole. Heats of mixing can also be interpolated at 20° from the results of Adcock and McGlashan.[8] Wood and Gray [9] measured the density of the mixture accurately from 15° to 75° and expressed their results as

$$100\Delta V_m/V_0 = \phi_1 \phi_2[0{\cdot}6763 - (0{\cdot}04362 + 0{\cdot}01335t)\phi_1]$$

where t is in °C. The vapour pressure of this mixture is almost ideal [10] and so $\beta_m \approx \beta_0$. Scatchard, Wood, and Mochel [10] use, at 25°,

$$\beta_m = 1{\cdot}10(1 + 0{\cdot}009\phi_2) \times 10^{-4}$$

The variation of β_m with concentration is so small that it may safely be neglected, and a constant value of $\beta_m = 1{\cdot}05 \times 10^{-4}$ has been employed for 20°.

Δv_m being expressed by an equation of the form of (2), $(\partial \Delta v_m/\partial \phi_1)_{P,T}$ was obtained for three values of ϕ_1, and $(\partial \Delta H_m/\partial \phi_1)_{P,T}$ calculated from (15*b*). With ΔH_m expressed in the form of (1),

$$(\partial \Delta H_m/\partial \phi_1)_{P,T} = A(1 - 2\phi_1) + B(6\phi_1 - 6\phi_1^2 - 1) + C(1 - 10\phi_1 + 24\phi_1^2 - 16\phi_1^3)$$

permitting evaluation of A, B, and C. Fig. 1 shows ΔH_m calculated in this way compared with the experimental results.[7,8] The agreement is excellent and justifies the neglect of

[7] Scatchard, Ticknor, Goates, and McCartney, *J. Amer. Chem. Soc.*, 1952, **74**, 3721.
[8] Adcock and McGlashan, *Proc. Roy. Soc.*, 1954, *A*, **226**, 266.
[9] Wood and Gray, *J. Amer. Chem. Soc.*, 1952, **74**, 3729.
[10] Scatchard, Wood, and Mochel, *ibid.*, 1939, **61**, 3206.

$(\partial\Delta H_m/\partial\phi_1)_{\Delta V_m, T}$ in (15*b*). Clearly also, the data employed permit an accurate calculation to be made. Table 1 show the parameters of (15*b*) where χ has been written for

$$\left[\frac{1}{100(\beta_0 V_0 - \beta_m V_m)}\right]_{T,\phi} \times [\Delta V_m - T(\partial\Delta V_m/\partial T)_{P,\phi}].$$

TABLE 1. *Parameters of equation* (15b) *for* cyclo*hexane–carbon tetrachloride* (20°).

ϕ_1	0·25	0·50	0·75
Δv_m	0·12351	0·16028	0·11693
$10^5(\partial\Delta V_m/\partial T)_{P,\phi}$	8·90	2·16	−4·66
χ (J)	7·72	9·28	10·77
$(\partial\Delta v_m/\partial\phi_1)_{P,T}$	0·3595	0·01758	0·3513

Benzene–toluene. This system has a very small heat of mixing which has been measured at 20° by Cheesman and Canning [11] and Mathieson and Thynne [2] and the results are in very good agreement. The latter give $\Delta H_m = x_1x_2[272 - 18{\cdot}8(x_1 - x_2) - 5{\cdot}4(x_1 - x_2)^2]$,

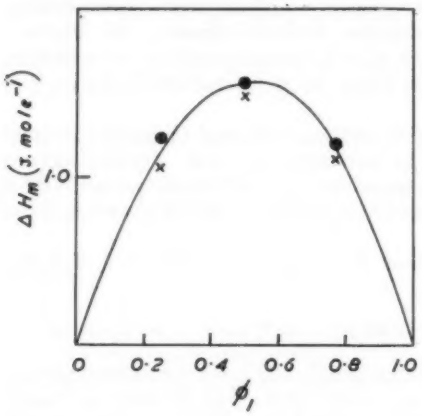
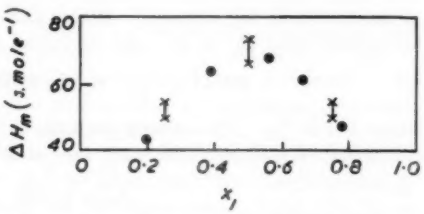


FIG. 1. *Carbon tetrachloride*—cyclo*hexane at* 20°.
● Results of Scatchard, Ticknor, Goates, and McCartney.
× Interpolated results of Adcock and McGlashan.
Full curve, calculated values from (15).

FIG. 2. *Benzene–toluene at* 20°.
● Results of Mathieson and Thynne.
× Calculated values showing limits of accuracy, from (15).



where ΔH_m is in J/mole, and x_1 is the mole fraction of benzene. Thynne [12] gives $100\Delta V_m/V_0 = x_1x_2[0{\cdot}60 + 0{\cdot}06(x_1 - x_2) - 0{\cdot}13(x_1 - x_2)^2]$ at 20°. The variation of ΔV_m with T can be calculated from the results of Kremann, Meingast, and Gugl [13] provided that only their values for 10°, 20°, and 30° are employed. Their results at higher temperatures, and the more recent determinations of Rastogi and Rama Varma [14] at 30°, are not sufficiently self-consistent to be used. The constant value of $\beta_m = \beta_0 = 0{\cdot}92 \times 10^{-4}$ was used since benzene, toluene, and their mixtures all show the same isothermal compressibility.[15] The values of $(\partial\Delta V_m/\partial T)_{P,x}$ are not so accurate as for the other systems

[11] Cheesman and Canning, *J.*, 1955, 1230.
[12] Thynne, Thesis, Nottingham, 1956.
[13] Kremann, Meingast, and Gugl, *Monatsh.*, 1907, **28**, 831.
[14] Rastogi and Rama Varma, *J.*, 1957, 2257.
[15] Gabrielli and Poiani, *Koninkl. Vlaam. Acad. Wetenschap.*, letter, en Schone Kunsten België, Colloquium, Ultrasonore, Trillingen, Brussels, 1951, 234; *Chem. Abs.*, 1952, **46**, 10,741.

XUM

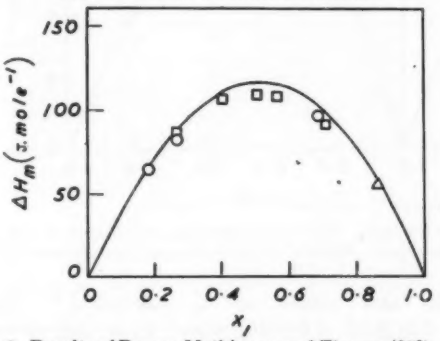
considered, and the limits so set to the accuracy of the calculation are shown in Fig. 2, in which ΔH_m calculated from (15*a*) is compared with the experimental results.[2] The values predicted are in accord with the experiments, and again $(\partial \Delta H_m/\partial P)_{\Delta V_m, T}$ is negligible. The parameters of (15*a*) are shown in Table 2. For this system and for ethanol–water and benzene–carbon tetrachloride, $\chi = [1/(\beta_0 V_0 - \beta_m V_m)][\Delta V_m - T(\partial \Delta V_m/\partial T_{P,x}]$.

TABLE 2. *Parameters of equation* (15a) *for benzene–toluene at* 20°.

x_1	0·25	0·50	0·75
ΔV_m	0·110	0·146	0·108
$10^4(\partial \Delta V_m/\partial T)_{P,x}$	5·5	7·0	5·5
χ(J)	510	460	540

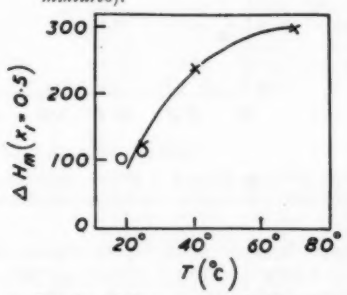
Carbon tetrachloride–benzene. This system has small heats[1,16,17] and volumes[18] of mixing but the vapour pressure deviates by about 4% from ideality at 25°.[22] Since ΔV_m is so small the difference between β_m and β_0, though small, is significant and β_m was calculated from (18) by using the vapour-pressure data of Scatchard, Mochel, and Wood,[22] specific volumes of vapour of 326 and 146 for benzene and carbon tetrachloride respectively

FIG. 3. *Carbon tetrachloride–benzene.*



○ Results of Brown, Mathieson, and Thynne (25°).
□ Results of Cheesman and Whitaker (24·7°).
△ Result of Hirobe (25°).
Full curve, calculated values (25°).

FIG. 4. *Effect of temperature for carbon tetrachloride–benzene (equimolar mixtures).*



○ Results of Cheesman and Whitaker.
× Calculated values.

TABLE 3. *Parameters of* (15a) *for carbon tetrachloride–benzene.*

x_1 (CCl_4)	0·25	0·50	0·75	ΔV_m at 25°	0·0106	0·0144	0·0110
$10^6(\beta_m - \beta_0)$ at 25°	0·040	0·043	0·044	,, 40°	0·0324	0·0373	0·350
,, 40°	0·023	0·028	0·024	,, 70°	0·0688	0·0867	0·0796
,, 70°	0	0	−0·015	χ (J) at 25°	8400	8130	8770
				,, 40°	6610	6310	7110
$(\partial \Delta V_m/\partial T)_{P,x}$ at 25—70°	0·00133	0·00153	0·00160	,, 70°	3860	3400	4330

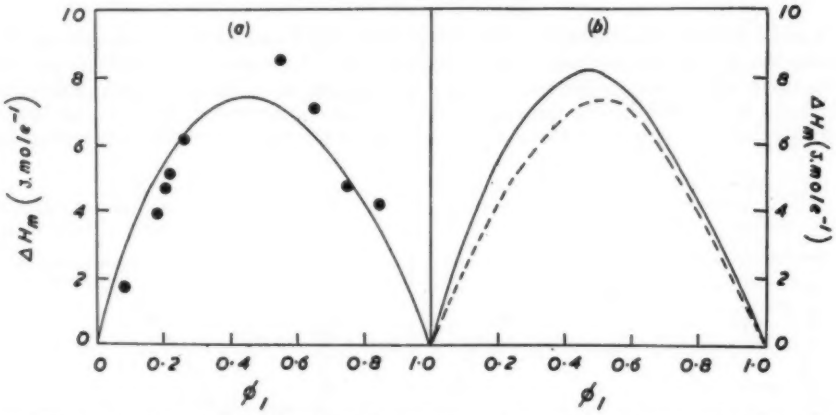
at N.T.P., specific volumes of the liquid mixtures at various temperatures determined by Wood and Brusie,[18] and the values of β_0 employed by the latter. Calculations were made for 25°, 40°, and 70° (Table 3). When $\beta_m - \beta_0$ is known accurately, uncertainty of a few units % in β_0 has negligible effect on (15*a*). Fig. 3 shows values of ΔH_m calculated from (15*a*) at 25° compared with the experimental results.[1,16,17] Agreement is very good. For this system, $\Delta V_m - T(\partial \Delta V_m/\partial T)_{P,x}$ is independent of temperature, having values of −0·385, −0·442, and −0·467 for $x = 0·25$, 0·50, and 0·75, respectively, for 25°, 40°, and 70°. The effect of temperature on ΔH_m is shown in Fig. 4, where values calculated from

[16] Cheesman and Whitaker, *Proc. Roy. Soc.*, 1952, *A*, **212**, 406.
[17] Hirobe, *J. Fac. Sci. Tokyo Univ.*, 1925, **1**, 155.
[18] Wood and Brusie, *J. Amer. Chem. Soc.*, 1943, **65**, 1891.

(15*a*) are compared with Cheesman and Whitaker's results.[16] The calculated values suggest that ΔH_m is not linear in T, but experimental determinations at higher temperatures would be desirable for confirmation.

Benzene–cyclo*hexane*. This system is far from ideal [19] and has a relatively large heat of mixing.[1] β_m was calculated from (18) by using the vapour-pressure data from Scatchard, Wood, and Mochel,[19] specific volumes of vapour of 326 and 302 for benzene and *cyclo*hexane respectively at N.T.P., specific volumes of the liquid mixtures at various temperatures determined by Scatchard, Wood, and Mochel,[19] Wood and Austin,[20] Mathieson and

FIG. 5. *Benzene*–cyclo*hexane*.



(*a*) 20°. ● Results of Brown, Mathieson and Thynne. Full curve, calculated values from (15).
(*b*) 40°. Broken curve, values calculated from vapour pressure. Full curve, calc. values from (15).

Thynne,[2] and some new measurements, and values of β_0 calculated [21] from $\beta_0 = 1{\cdot}02(1 + 0{\cdot}12\phi_2) \times 10^{-4}$ at 30° and $\mathrm{d}\ln\beta/\mathrm{d}T = 0{\cdot}0076$, where ϕ_2 is the volume fraction of *cyclo*hexane. The values of β_m fall on a convex-upwards curve with ϕ and are up to 2·5% greater than β_0 (Table 4). All the data being considered, the excess volume was expressed as

$$100\Delta V_m/V_0 = \phi_1\phi_2[3{\cdot}28 - 0{\cdot}587(\phi_1 - \phi_2) - 0{\cdot}174(\phi_1 - \phi_2)^2] \quad (40°)$$
$$100\Delta V_m/V_0 = \phi_1\phi_2[2{\cdot}32 - 0{\cdot}481(\phi_1 - \phi_2) - 0{\cdot}427(\phi_1 - \phi_2)^2] \quad (20°)$$

ΔH_m was calculated from (15*b*), the parameters of which are shown in Table 4. Fig. 5*a* shows the calculated values compared with the experimental results of Brown, Mathieson,

TABLE 4. *Parameters of equation* (15b) *for benzene*–cyclo*hexane*.

ϕ_1	0·25	0·50	0·75	ΔV_m (40°)	0·700	0·823	0·523
$10^4\beta_m$ (20°)	103·9	101·3	98·5	$(\partial\Delta V_m/\partial T)_{P,\phi}$ (20°, 40°)	0·0108	0·0137	0·0092
$10^4\beta_m$ (40°)	120·8	117·9	114·2	χ (20°) (J)	10·84	12·52	13·22
ΔV_m (20°)	0·483	0·550	0·340	χ (40°) (J)	9·71	9·86	10·40

and Thynne [1] at 20°. Agreement is good, though not so good as for benzene–carbon tetrachloride and carbon tetrachloride–*cyclo*hexane, but the experimental results are more scattered for the present system. ΔH_m calculated at 40° can only be compared with the values calculated by Scatchard, Mochel, and Wood [22] from vapour-pressure measurements

[19] Scatchard, Wood, and Mochel, *J. Phys. Chem.*, 1939, **43**, 119.
[20] Wood and Austin, *J. Amer. Chem. Soc.*, 1945, **67**, 480.
[21] International Critical Tables, Nat. Acad. Sci., U.S.A., 1928.
[22] Scatchard, Mochel, and Wood, *J. Amer. Chem. Soc.*, 1940, **62**, 712.

and this comparison is shown in Fig. 5*b*. The calculation of heats of mixing from vapour-pressure measurements is uncertain owing to the variation of the heat of mixing with temperature,[1,23] but nevertheless the two sets of values are in reasonable accord.

Ethanol–water. Many accurate data are available for this system, for which the form of the variation of ΔH_m and ΔV_m with x indicates that $(\partial \Delta H_m/\partial x)_{\Delta V_m, T}$ is not zero. Isothermal compressibilities were calculated from Giacomini's sound velocities (u),[24] the coefficients of expansion (a) calculated from the densities (d_m),[21] and the specific heats at constant pressure (C_p) [21] by using

$$\alpha = 1/d_m u^2 \text{ and } \beta = \alpha + aT/C_p d_m$$

where α is the adiabatic compressibility. The results (Table 5) have minima between $x_1 = 0{\cdot}05$ and $0{\cdot}11$ corresponding to the maxima of the sound velocities. At values of x_1 greater than those corresponding to the minima, β_m increases with T but it decreases with T at lower values of x_1. ΔV_m and $(\partial \Delta V_m/\partial T)_{P,x}$ were calculated from the density compilation [21] and are shown with the other parameters of (15*a*) in Table 6.

TABLE 5. *Isothermal compressibilities of ethanol–water.*

Mole fraction of EtOH (x_1)	$10^6\beta_m$ 10°	20°	30°	40°	Mole fraction of EtOH (x_1)	$10^6\beta_m$ 10°	20°	30°	40°
0·0000	47·39	45·66	44·66	44·00	0·370	59·97	62·82	66·04	70·07
0·0416	42·52	41·92	41·80	42·08	0·477	67·21	71·39	75·49	79·36
0·0890	39·57	40·65	41·86	43·15	0·610	75·53	80·22	85·31	90·69
0·144	40·89	42·77	44·91	47·27	0·779	86·08	92·24	98·61	105·41
0·207	45·63	48·02	50·81	53·70	1·000	102·11	109·82	118·16	127·36
0·281	52·92	54·35	57·86	61·77					

TABLE 6. *Parameters of equation* (15a) *for ethanol–water.*

x_1	0·0416	0·0891	0·144	0·207	0·281	0·370	0·447	0·610	0·778
$-\Delta V_m$ at 20°	0·1884	0·4600	0·7250	0·9170	0·0372	1·0976	1·0935	0·9919	0·7114
,, 30°	0·1972	0·4563	0·7004	0·8812	0·9995	1·0629	1·0627	0·671	0·6943
$T(\partial \Delta V_m/\partial T)_{P,x}$ at 20°	−0·288	0·119	0·810	1·174	1·211	1·114	0·957	0·762	0·467
,, 30°	−0·242	0·108	0·681	0·990	1·056	0·994	0·906	0·758	0·523
χ (J) at 20°	−75·2	235	494	658	690	757	809	645	510
,, 30°	−36·2	256	616	688	744	740	853	633	541

Clearly, $(\partial \Delta H_m/\partial x_1)_{\Delta V_m, T}$ is not zero, so ΔH_m cannot be calculated from (15*a*). However, plots of $\chi.(\partial \Delta V_m/\partial x_1)_{P,T}$ against x_1 at 20° and 30° give curves of similar shape to plots of ΔH_m against x_1 constructed from Bose's data [25] at the same temperature. Both sets of curves rise to a maximum at $x_1 = 0{\cdot}15$ and then fall gradually, showing the same minor inflexion between $x_1 = 0{\cdot}55$ and $0{\cdot}85$. This striking similarity implies that, to a first approximation,

$$\chi(\partial \Delta V_m/\partial x_1)_{P,T} = k_1.\Delta H_m + k_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

where $k_1 = 3{\cdot}7$ (20°) and $5{\cdot}7$ (30°) and $k_2 = 2000$ J. Fig. 6 shows plots of $\chi(\partial \Delta V_m/\partial x_1)_{P,T}$ and $k_1.\Delta H_m + k_2$ against x_1. Equation (19) makes it possible to calculate values of ΔH_m for any concentration from measurements of density and compressibility provided ΔH_m is known experimentally at a single concentration. Its theoretical significance is obscure. By combination with (15*a*),

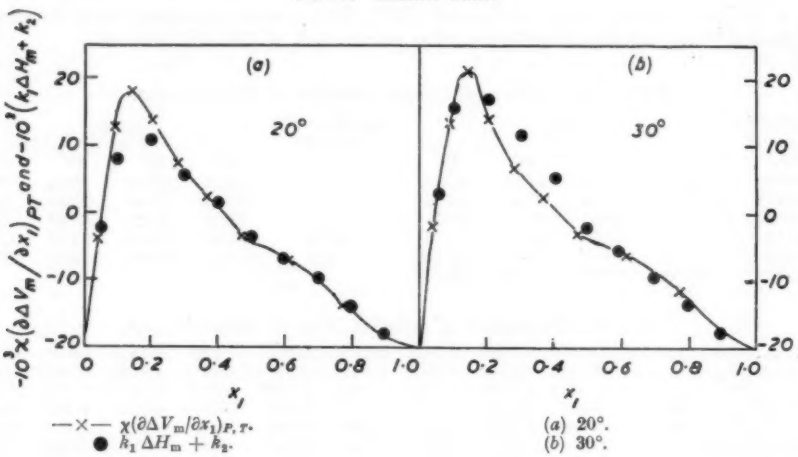
$$k_1.\Delta H_m + k_2 = (\partial \Delta H_m/\partial x_1)_{P,T} - (\partial \Delta H_m/\partial x_1)_{\Delta V_m, T} \quad . \quad . \quad . \quad (20)$$

It is not yet known whether (19) and (20) are peculiar to this system, or are applicable to polar mixtures in general.

[23] Cheesman and Ladner, *Proc. Roy. Soc.*, 1955, *A*, **229**, 337.
[24] Giacomini, *J. Acoust. Soc. Amer.*, 1947, **19**, 701.
[25] Bose, *Z. phys. Chem.*, 1907, **58**, 585.

Discussion.—The excess heat and volume of mixing are related *via* their differentials with concentration by expressions involving the change of excess volume with temperature and the excess compressibility. Provided the mixtures chosen can be regarded as typical of their groups of mixtures, it may be concluded that for binary mixtures which depart from ideality (as determined by their vapour pressure) by less than ~2% it is possible to calculate the heat of mixing from density measurements and the compressibilities of the pure components. For binary mixtures which show greater positive departures from ideality the compressibility of the mixtures needs also to be known, or it can be calculated from the vapour pressures. For ethanol–water a value of ΔH_m at a single concentration is also required. Conversely, in the last two cases if the heats of mixing are known the compressibilities of the mixtures can be calculated.

FIG. 6. *Ethanol–water.*



—×— $\chi(\partial\Delta V_m/\partial x_1)_{P,T}$.
● $k_1\Delta H_m + k_2$.

(*a*) 20°.
(*b*) 30°.

The equations presented here may be compared with the various theories of mixtures. Scatchard [26] and Hildebrand and Scott [27] concluded that ΔH_m and ΔV_m were interdependent for non-polar solutions. The extension of the treatment of regular solutions by Scott [5] to include volumes of mixing led to equations for $\Delta V_m/V_m$ and $\Delta H_m/N$ (N = Avogadro's number) which when combined yield

$$\Delta H_m/N = \frac{\Delta V_m}{\beta_m V_m}\left[T(\partial V_m/\partial T)_p - \frac{\varepsilon\beta_m V_m}{T(\partial V_m/\partial T)_p}\right] \quad . \quad . \quad . \quad . \quad (21)$$

where ε is the molecular interaction energy. When (15*a*) is applied to regular solutions, ΔH_m and ΔV_m may be written for $(\partial\Delta H_m/\partial x)_{P,T}$ and $(\partial\Delta V_m/\partial x)_{P,T}$ since ΔH_m and ΔV_m are proportional functions of x. Equation (21) is evidently related to (15*a*) and predicts proportionality of ΔH_m and ΔV_m. The first-order conformal solution treatment of Longuet-Higgins [28] gives equations for $\Delta V_m/V_m$ and $\Delta H_m/N$ which on combination yield

$$\Delta H_m/N = \Delta V_m \cdot \frac{1}{T}\left(\frac{\partial T}{\partial V_0}\right)\left[T\left(\frac{\partial \varepsilon_0}{\partial T}\right) - \varepsilon_0\right] \quad . \quad . \quad . \quad . \quad (22)$$

where ε_0, V_0 refer to the reference substance. This also predicts proportionality of ΔH_m and ΔV_m. Prigogine and Mathot's [6] "smoothed potential" (square-well potential) cell

[26] Scatchard, *Trans. Faraday Soc.*, 1937, **33**, 160.
[27] Hildebrand and Scott, "Solubility of Non-electrolytes," Reinhold, New York, 1950, pp. 138—143.
[28] Longuet-Higgins, *Proc. Roy. Soc.*, 1951, *A*, **205**, 247.

XUM

model gives ΔV_m proportional to the other excess functions of mixing for non-polar mixtures, and for other mixtures also provided second-order terms are neglibible. Sarolea [29] considered that non-random mixing (excluded from the original theory) would not affect the conclusions. Pople,[30] employing the cell field of Lennard-Jones and Devonshire [31] and allowing for non-random mixing, found ΔV_m a function of ΔF_m for first-order interactions. All these theories agree that, for first-order interactions, ΔV_m is a function of ΔH_m, which is equivalent to setting $(\partial \Delta H_m/\partial x)_{\Delta V_m, T} = 0$ in (15*a*). With this condition, (15*a*) is applicable to four non-polar solutions but not to ethanol–water, and it may well hold for first-order interactions in general. It is tempting to suggest that $(\partial \Delta H_m/\partial x)_{\Delta V_m, T}$ may account for second- and higher-order interactions.

Recently, some more general corresponding-states treatments of non-electrolyte solutions have appeared.[32,33] Scott, for two types of cell (the "two-liquid" approach, equivalent to that of Prigogine *et al.*), gives expressions for ΔH_m in terms of the excess energy of vaporisation ($\overline{E}'$), $(\partial \overline{E}'/\partial T)$, and $(\partial^2 \overline{E}'/\partial T^2)$, molecular parameters and difference functions, and for ΔV_m in terms of V_m, $(\partial V_m/\partial T)$, $(\partial^2 V_m/\partial T^2)$, molecular parameters, and difference functions. By treating $\overline{E}'$ as an excess internal latent heat at constant zero pressure, relationships between $\overline{E}'$ and V_m, and the corresponding temperature derivatives, can be established involving ΔV_m, $\Delta(\beta V)$, a, and their temperature derivatives. In this way it can be shown that the theory leads to

$$\Delta H_m = \Delta V_m \left(\frac{1}{\beta_0 V_0 - \beta_m V_m}\right)\left[\Delta V_m - T\left(\frac{\partial \Delta V_m}{\partial T}\right)_P - T^2\left(\frac{\partial \Delta V_m}{\partial T}\right)^2_P\right] j + \Delta V_m - x_1 x_2 f(V_m, \beta_m, a, T, j') \quad . \quad . \quad (23)$$

where j, j' have been written for different combinations of the molecular parameters and difference functions. Equation (23) is more closely related to (15*a*) than the earlier theoretical equations, (21) and (22). Part of the last term in (23) is independent of ΔV_m and so corresponds to $(\partial \Delta H_m/\partial x)_{\Delta V_m, T}$. The expressions of Prigogine *et al.* are in such a form as not to lend themselves so readily to comparison with the present theory.

Experimental

Experimental.—The densities of benzene–*cyclo*hexane mixtures were measured at 35° ± 0·02° and 45° ± 0·02°, and the excess volumes calculated (Table 7). The results are in good agreement with earlier determinations.[2,19,20] The liquids were purified as already described, and

Table 7. *Densities and excess volumes of benzene–*cyclo*hexane.*

35°			45°		
x_1	d_m	ΔV_m	x_1	d_m	ΔV_m
0·0	0·76522	—	0·0	0·75456	—
0·28792	0·78566	0·674	0·28792	0·77486	0·724
0·54978	0·80930	0·775	0·54801	0·79780	0·891
0·78761	0·83550	0·434	0·78576	0·83275	0·594
1·00000	0·86182	—	1·00000	0·85172	—

their properties have been listed.[1] A 20 ml. pyknometer, of dilatometer pattern, viewed through a cathetometer, was employed. It was calibrated with water.

I am grateful to Professor H. T. Flint for valuable discussions.

University College, Ibadan, Nigeria. [*Received, June 13th*, 1958.]

[29] Sarolea, *J. Chem. Phys.*, 1953, **21**, 182.
[30] Pople, *Trans. Faraday Soc.*, 1953, **49**, 591.
[31] Lennard-Jones and Devonshire, *Proc. Roy. Soc.*, 1937, *A*, **163**, 63.
[32] Prigogine, Bellemans, and Englert-Chwoles, *J. Chem. Phys.*, 1956, **24**, 518.
[33] Scott, *ibid.*, 1956, **25**, 193.

XUM

899. *Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part XV.* Some New 3 : 3′-Disubstituted Naphthidines.*

By R. Belcher, S. J. Lyle, and W. I. Stephen.

The redox properties of a number of new 3 : 3′-disubstituted naphthidines and their applications as analytical reagents have been examined. Spectrophotometric data for the oxidised naphthidines, sensitivities towards oxidants, and transition potentials are given for the reactive compounds. Their behaviour as indicators in several conventional titrations is described.

It has been shown that naphthidine [1] and 3 : 3′-dimethylnaphthidine [2] can be used advantageously as reversible chemical indicators in certain redox titrations. The dimethyl derivative was found to be about ten times as sensitive to oxidants as the parent base, and its oxidised form was considerably more stable than that of naphthidine. We have now examined several substituted naphthidines in an attempt to correlate their redox properties with the nature of the substituent group. A range of substituted naphthidines having, in the 3- and 3′-position, the groups Et, Pr^n, Pr^i, OMe, Ph, NO_2, NH_2, and SO_3H, has been prepared [3] and their properties of interest in analytical processes are described. The redox properties of these new compounds have been studied spectrophotometrically and potentiometrically, and a comparison has been made with established indicators to assess their suitability for some practical applications.

Colour Reactions and Sensitivity Tests.—In aqueous acid solutions of many oxidants, naphthidine and substituted naphthidines undergo reversible oxidation to highly coloured soluble substances of varying stability. The colour reactions observed with the series under consideration are summarised in Table 1.

Table 1.

Reagent, R =	Colour change, Colourless to:	Reagent, R =	Colour change, Colourless to:
H	Bordeaux red	Ph	Violet
Me, Et, Pr^n, Pr^i, SO_3H	Purple-red	NO_2	No apparent reaction
OMe	Greenish-blue	NH_2	Transient green, brown ppt.

(Here and in subsequent Tables, the naphthidine is represented by the substituent R in the 3- and the 3′-position.)

3 : 3′-Dinitronaphthidine is not oxidised by any common inorganic oxidant, including perchloric acid solutions of cerium(IV). The diamino-derivative is extremely sensitive to oxidants but is probably oxidised, unlike other naphthidines, to a dinaphthadiquinone. The disulphonic acid is oxidised to a stable coloured product only in acid solutions more concentrated than 2M. The sensitivities of the reactive naphthidines to various oxidants have been determined in 0·1N-hydrochloric acid. The low solubility of the free amines in water made it necessary to confine the measurements to solutions in acid. Oxidation at low concentrations of oxidants was slow and might easily be confused with aerial oxidation of the amines, so that a limiting reaction time was necessary in determining the sensitivities. The minimum amount of oxidant detected within two minutes of mixing is given in Table 2.

The diphenyl and dimethoxy-derivatives have slightly lower sensitivities than the dialkyl derivatives, all of which have the same sensitivity towards the oxidants used. In this comparison the disulphonic acid is at a disadvantage because it is oxidised to a stable coloured product only in solutions of acidity 2M or greater, in which the sulphonic acid

* Part XIV, *J.*, 1958, 2336.

[1] Belcher and Nutten, *J.*, 1951, 548.
[2] Belcher, Nutten, and Stephen, *J.*, 1951, 1520, 3444.
[3] Belcher, Lyle, and Stephen, *J.*, 1958, 3243.

groups are presumably un-ionised. The higher sensitivity towards iron(III) in 0·1N-acid than to other ions can then be explained through ferric ions' acting as electron-acceptors for the ionised sulphonic acid groups, as does the hydrogen ion at high acid concentrations.

TABLE 2.

Reagent, R =	Identification limit (μg.) in 2 ml. of solution.							
	$Cr_2O_7^{2-}$	IO_3^-	$S_2O_8^{2-}$	VO_3^-	$Fe(CN)_6^{3-}$	IO_4^-	Fe^{3+}	OCl^-
H	2	0·8	60	20	0·9	10	—	0·9
Me, Et, Pr^n, Pr^i	0·2	0·2	2	1	0·1	0·1	1	0·1
OMe	0·2	0·5	10	1	0·1	0·2	1	0·1
Ph	0·2	0·8	2	1	0·1	0·6	1	0·1
SO_3H	—	—	—	30	20	20	1	0·9

Spectrophotometric Measurements.—The coloured oxidised naphthidines are generally sufficiently stable for absorption spectra to be plotted in the visible region. The spectra of the oxidised naphthidines are independent of the oxidant used, but an increase in acid concentration causes a slight shift of maximum absorption to longer wavelengths (Table 3) and produces a visible change in colour. A quantitative comparison of the colour stability of the oxidised naphthidines under standardised reaction conditions has been made; by observing the change in optical density at the wavelength of maximum absorption during 5—6 hours, the dialkyl- and diphenyl-substituted naphthidines are shown to have similar stabilities, the decrease in optical density being 0·025 to 0·045 for solutions of optical densities 0·2 to 0·8. In contrast, oxidised naphthidine solutions under the same conditions were decolorised completely within 10 minutes and the dimethoxy-derivative within 20 minutes. At acidities above 4M, the disulphonic acid gave colours which were about half as stable as those of the dialkyl derivatives. The optical densities of 1% solutions of the oxidised amines for a path length of 1 cm. ($E_{1\text{ cm.}}^{1\%}$) were then determined. Results were reproducible for replicate determinations using the same oxidant, different oxidants, and varying amounts of amine. Variation in the strength of sulphuric acid (0·5—4M) gave the same calculated $E_{1\text{ cm.}}^{1\%}$ values within the experimental error (±20). The molecular extinction coefficients (ε) of the oxidised naphthidines have been calculated from the $E_{1\text{ cm.}}^{1\%}$ values on the assumption that oxidation does not significantly affect the molecular weights.

TABLE 3. *Spectrophotometric properties of oxidised naphthidines.*

Reagent, R =	$\lambda_{max.}$ (mμ) in M-H_2SO_4	$\lambda_{max.}$ (mμ) in 4M-H_2SO_4	$10^{-3}\varepsilon$
H	530	535	29
Me	550	560	30
Et	550	560	30
Pr^n	550	560	31
Pr^i	550	560	26
OMe	615	—	—
Ph	570	575	21
SO_3H	—	560	—

These oxidised naphthidines have similar absorption bands in the visible region and therefore their molecular extinction coefficients may be taken as a measure of their sensitivities towards oxidants. The low value for 3 : 3′-diphenylnaphthidine is supported by its lower sensitivity (Table 2) towards oxidants. This naphthidine might be expected to have a larger molecular extinction coefficient than dialkylnaphthidines through conjugation of the phenyl and the naphthalene nucleii. That this is not so suggests that coplanarity of the phenyl groups with the oxidised naphthidine nucleus is sterically prevented. Steric effects may also be partially responsible for the greater stability of the coloured oxidised 3 : 3′-disubstituted naphthidines than of naphthidine; the substituents could have a shielding effect on the sensitive oxidised amino-groups. The instability of oxidised 3 : 3′-dimethoxynaphthidine to light of wavelength near its absorption maximum prevented its being included in this study.

Measurement of Oxidation Potentials.—Belcher, Nutten, and Stephen [4] described the determination of the oxidation potentials of naphthidine, its 3 : 3'-dimethyl homologue, and their sulphonated derivatives, but they found that the oxidised naphthidine and its sulphonated product were too unstable for such work. As an alternative, they determined the potentials at which colour formation was first observed (transition potentials). Stockdale,[5] in his comparative study of indicators for the iron(II)–dichromate titration, as well as determining the transition potentials, determined the potentials of maximum colour formation. The latter is an important property since, together with the transition potential, it determines the potential range over which the indicator is progressively oxidised or reduced in a given redox system. The transition potentials of the present series of naphthidines were initially determined for the Fe^{2+}–Fe^{3+} and $Cr_2O_7^{2-}$–Cr^{3+} systems, with diphenylamine-4-sulphonic acid as a control. The greenish-blue colour of dimethoxynaphthidine on oxidation excluded it from this series of measurements. On adding an excess of dichromate to an acid solution of a naphthidine, it was found that the colour did not develop markedly until a few drops of a ferrous iron solution were added, a phenomenon previously observed with diphenylamine.[6] Because of these factors and the complicated non-reversible reduction of dichromate to chromic ions,[7] the transition measurements were repeated in the Fe^{2+}–Fe^{3+} and the Ce^{4+}–Ce^{3+} system. The results for both series of measurements are recorded in Table 4 for various concentrations of sulphuric acid.

TABLE 4. *Transition potentials* (±0·01 V) *at* 20°, *referred to the standard hydrogen electrode.*

Indicator, R =	Acid concentration (M) (H_2SO_4)				
	0·1	0·5	1·0	2·0	4·0
H	0·80	0·81	0·79	0·78	0·76
		(0·79)	(0·79)	(0·76)	(0·74)
Me	0·69	0·71	0·71	0·71	0·70
		(0·70)	(0·70)	(0·70)	(0·67)
Et	0·70	0·72	0·72	0·72	0·72
		(0·72)	(0·71)	(0·72)	(0·69)
Pr^n	0·70	0·72	0·72	0·72	0·72
		(0·72)	(0·71)	(0·72)	(0·69)
Pr^i	0·73	0·75	0·75	0·75	0·74
		(0·74)	(0·74)	(0·74)	(0·72)
Ph	0·75	0·76	0·76	0·76	0·76
		(0·76)	(0·76)	(0·75)	(0·73)
SO_3H	—	—	0·83	0·83	0·83
		(0·86)	(0·86)	(0·85)	(0·85)
OMe	—	(0·74)	(0·74)	(0·73)	(0·70)

(Values in parentheses are those for the Fe^{2+}–Fe^{3+} and the Ce^{4+}–Ce^{3+} systems.)

Replacement of dichromate by ceric ions as oxidant gave slightly lower values for the transition potentials. The inductive effect of ferrous ions in the dichromate–chromic system was not observed in ceric–cerous systems containing naphthidines. It has been suggested [6] that the ferrous iron is momentarily oxidised to a higher unstable oxidation state which is responsible for the rapid oxidation of the indicator. It seems more likely that an unstable intermediate reduction product in the dichromate–chromic system, perhaps quinquevalent chromium, is responsible.[7]

The observed order (Table 4) for the transition potentials is $SO_3H > H > Ph > Pr^i > OMe > Pr^n$, Et > Me at each acid concentration and for each inorganic redox system investigated. It is probable that both electronic [8] and steric effects are largely responsible for the observed values, but as yet the information obtained is not sufficient to allow the relative importance of these effects to be estimated.

[4] Belcher, Nutten, and Stephen, *J.*, 1952, 3857.
[5] Stockdale, *Analyst*, 1950, **75**, 150.
[6] Kolthoff and Sarver, *J. Amer. Chem. Soc.*, 1930, **52**, 4181.
[7] Kolthoff and Sandell, "Textbook of Quantitative Inorganic Analysis," The Macmillan Co., New York, 3rd edn., 1952, p. 466.
[8] Fieser, *J. Amer. Chem. Soc.*, 1930, **52**, 5204.

Stockdale did not indicate how he determined the potential at maximum development of colour. In this work, the indicator solution containing iron(II) was oxidised with either a dichromate or a ceric solution and the colour intensity compared visually with that of a similar solution in which the indicator was fully oxidised; the oxidation potential was then measured when maximum colour formation had taken place. The potentials were the same for both oxidants within the estimated experimental error (±0·01 V), and the value found for diphenylamine-4-sulphonic acid was the same as that found by Stockdale. Results are in Table 5.

The potential range within which the colour change of the indicators took place in M-sulphuric acid (transition interval) was obtained by subtracting the mean value of the

TABLE 5 *Potentials (in volts, referred to the hydrogen electrode) of maximum colour intensity at 20°.*

Indicator, R =	*	H	CH_3	C_2H_5	C_3H_7	C_5H_7	OCH_3	C_6H_5	SO_3H
Potential	0·91	0·83	0·85	0·90	0·90	0·91	0·88	0·94	0·91
Transition interval...	0·09	0·04	0·14	0·18	0·18	0·16	0·14	0·18	0·06

* Diphenylamine-4-sulphonic acid.

transition potential (Table 4, column 4) from the appropriate potential of maximum colour intensity. It is probable that the indicator solubility plays a part in determining the " transition interval." The more soluble sulphonic acids have appreciably lower ranges than other substituted naphthidines. This is supported by Stockdale's results for diphenylamine and *NN'*-diphenylbenzidine which theoretically should have the same transition potential but have different potentials of maximum colour intensity (0·86 and 0·94 V, respectively). Further support is provided by potentiometric titration of dimethylnaphthidine in a mixture of 50% aqueous acetic acid and 4M-sulphuric acid. A two-electron change is involved in the oxidation to the stable purple-red compound and the " transition interval " is only 0·05 V. This suggests that an indicator having an oxidation potential lower than that corresponding to the equivalence point in a redox titration may still function satisfactorily if its solubility is not too great.

Analytical Applications.—Straka and Oesper [9] recommended naphthidine as an internal indicator in the titration of iron(II) with dichromate. Although the colour change is reversible, the indicator response is sluggish and the colour less stable than that of the conventional indicator, diphenylamine-4-sulphonic acid. The main disadvantages of the latter are its dependence on acid concentration and its high " blank " values. Kolthoff and Sarver [10] recommended that it be used only in 0·25—3N-acid. Naphthidine-3 : 3'-disulphonic acid, while oxidised in the same potential range (Tables 4 and 5), functions at higher acid concentrations and gives lower " blank " values. A comparison between the two compounds as indicators in this titration showed that naphthidinedisulphonic acid was a satisfactory indicator in 4—12M-acid, giving end-points to within one drop of 0·1N-dichromate and indicator " blank " values from one-half to two-thirds of those obtained with diphenylamine-4-sulphonic acid in 0·5—2M-acid. The naphthidinedisulphonic acid does not function in this titration in the presence of phosphoric acid. It may be of use as an internal indicator in vanadatometric procedures in which high acid concentrations are often necessary.[11]

New and improved indicators have been recommended for the titration of zinc and cadmium with ferrocyanide in the presence of ferricyanide. A comparison has been made between the naphthidines in titrations of this type under the conditions used by Belcher, Nutten, and Stephen.[2] Although satisfactory, they showed no marked advantages over 3 : 3'-dimethylnaphthidine. Naphthidinedisulphonic acid does not function under the titration conditions.

[9] Straka and Oesper, *Ind. Eng. Chem., Analyt.*, 1934, **6**, 405.
[10] Kolthoff and Sarver, *J. Amer. Chem. Soc.*, 1931, **53**, 2906.
[11] P. Rao, Murty, and G. Rao, *Z. analyt. Chem.*, 1955, **147**, 161.

In the titration of cadmium with ferrocyanide, the new dialkyl- and dimethoxy-naphthidines gave end-points as satisfactory as did 3 : 3′-dimethylnaphthidine, but with no marked advantages. The diphenyl and disulphonic acid derivatives were unsatisfactory, the former because of a sluggish colour-formation and the latter because of its colour-instability.

Experimental

Indicator Solutions.—A 0·2% aqueous solution of disodium naphthidinedisulphonate and 0·2% solutions of the other naphthidines in glacial acetic acid were used.

Oxidising Agents.—Stock solutions of $Cr_2O_7^{2-}$, IO_3^-, IO_4^-, $S_2O_8^{2-}$, VO_3^-, $Fe(CN)_6^{3-}$, Fe^{3+}, and OCl^- were prepared containing 1 mg. of the required ion per ml. Weaker solutions were made by dilution of the stock solution. The oxidants were of " AnalaR " purity except the hypochlorite.

Sensitivity Tests.—1 ml. of the neutral oxidant solution and 1 ml. of 0·2N-hydrochloric acid were added to a small test-tube (3″ × $\frac{3}{8}$″ diameter), followed by 1 drop of the organic reagent solution, and the whole was mixed. The oxidant concentration in the test solution was reduced until there was no longer any response from the reagent within 2 minutes of mixing. Blank tests, in which the oxidant was replaced by distilled water, were run concurrently.

Absorption Spectra.—0·2 ml. of a solution of the naphthidine in glacial acetic acid (1—1·5 g./l.) was mixed with 75 ml. of M-sulphuric acid. A slight excess of N-hypochlorite was added and the volume made up to 100 ml. After the colour had fully developed, the absorption spectrum was measured with a Unicam S.P. 600 spectrophotometer. $E^{1\%}_{1\,cm.}$ values at $\lambda_{max.}$ were obtained to provide the ε values given in Table 3.

Transition Potentials.—The apparatus, reagents, and procedure have been described in Part XI.[12]

Potentials of Maximum Colour Development.—To each of two 250-ml. beakers, 5 ml. of 0·1N-iron(II) solution in M-sulphuric acid, 95 ml. of the same acid, and two drops of the required indicator solution were added. One of the solutions was then oxidised fully with the selected oxidant. This solution was used for comparison, the potential of the other being gradually raised, first with 0·1N-, then 0·01N- or 0·001N-oxidant, until the colour had developed to the same extent; the potential was then noted.

Direct Titration of Dimethylnaphthidine.—The weighed amount (10—15 mg.) of pure amine was dissolved in warm acetic acid (50 ml.), and 4M-sulphuric acid (50 ml.) was added. The solution was cooled and titrated potentiometrically with standard 0·1N-cerium(IV).

The University, Birmingham. [*Received, June 27th,* 1958.]

[12] Belcher, Nutten, and Stephen, *J.*, 1952, 3861.

---

900. *Pharmacodynamic Compounds. Part I. Some Antispasmodics derived from Substituted 2-Pyrrolidinylalkanols.*

By F. P. Doyle, M. D. Mehta, G. S. Sach, and (in part) J. L. Pearson.

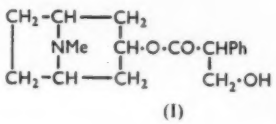
The preparation of some 1-alkyl-2-pyrrolidinylalkanols is described. These have been used to prepare a number of esters of diphenylacetic, benzilic, fluorene-9-carboxylic, and xanthen-9-carboxylic acid. Acid addition and quaternary ammonium salts of these esters have been prepared. Some have antispasmodic (antiacetylcholine) activity.

Numerous compounds modelled on the structure of atropine (I) have been synthesised in attempts to find compounds with the same desirable effects on the gastro-intestinal tract, but without some of the side-effects possessed by the parent alkaloid. In nearly all these compounds, the basic nitrogen atom forms part of either a substituted amino-group as in (II) or a simple heterocyclic group (pyrrolidine, piperidine, morpholine) in which the alkyl side chain is attached to the heterocyclic nitrogen atom as in (III).

The structure of the tropine moiety of atropine bears an obvious relation to the

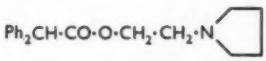
XUM

piperidinol (IV) and pyrrolidinylalkanols (V), noted by Burtner and Brown.[1] However, although a number of workers [2] have prepared atropine-like esters incorporating the piperidinol structure, it is only recently that Blicke and Lu [3] have prepared esters incorporating the pyrrolidinylmethanol (V; $R^1 = H$, $R^2 = Me$; $n = 1$). Their publication appeared during a systematic study of esters of (V) which was carried out in these Laboratories during the last four years and part of which is the subject of this communication.

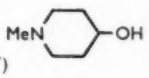


(I)

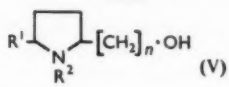
$Ph_2CH{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2$ (II)



(III)



(IV)



(V)

Methyl pyrrole-2-carboxylate was prepared by diazomethane from pyrrole-2-carboxylic acid which was obtained by a modification of Oddo's method.[4] The direct preparation of the ethyl ester by the method of Maxim *et al.*,[5] gave only small yields of an impure product. The potassium derivative of the methyl ester with excess of methyl iodide in toluene gave methyl 1-methylpyrrole-2-carboxylate which on reduction with lithium aluminium hydride gave, in excellent yield, 2-hydroxymethyl-1-methylpyrrole, obtained recently by Ryskiewicz and Silverstein [6] by reduction of 2-formyl-1-methylpyrrole with sodium borohydride. However, on attempting to dissolve the alcohol in glacial acetic acid for hydrogenation, it polymerised explosively: Ryskiewicz and Silverstein [6] also comment on the ease of polymerisation of this alcohol under comparatively mild conditions such as shaking its ethereal solution with aqueous sodium hydrogen sulphite. Hydrogenation in methanol (platinic oxide catalyst) under pressure did not proceed at room temperature, and at 168° after 21 hr. a very small amount of the required 2-hydroxymethyl-1-methylpyrrolidine was obtained, identified as a picrate identical with that obtained by Renshaw and Cass.[7]

This alcohol was finally obtained directly by the reduction of diethyl pyrrolidine-1 : 2-dicarboxylate [8] with lithium aluminium hydride by analogy with the work of Dannley *et al.*[9] who reported excellent yields of methylated amines on reduction of the corresponding urethanes.

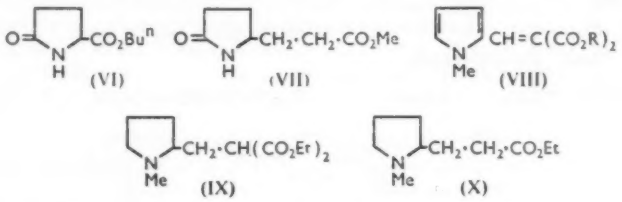
As an alternative route, butyl 5-oxopyrrolidine-2-carboxylate (VI) prepared from L-glutamic acid was reduced with lithium aluminium hydride in ether to 2-hydroxymethylpyrrolidine (V; $R^1 = R^2 = H$; $n = 1$) in 70% yield.[10] Methylation by formaldehyde and formic acid then gave 2-hydroxymethyl-1-methylpyrrolidine (V; $R^1 = H$, $R^2 = Me$; $n = 1$). Blicke and Lu [3] have described a similar method for the preparation of this alcohol.

2-(2-Hydroxyethyl)-1-methylpyrrolidine (V; $R^1 = H$, $R^2 = Me$; $n = 2$) was prepared by Hess, Merck, and Ulbrig,[11] but in view of the difficulties experienced in the preparation

[1] Burtner and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 630.
[2] Burtner and Cusic, *ibid.*, 1943, **65**, 262; Burtner, U.S.P. 2,387,879/1945; Biel, Friedman, Leiser, and Sprengler, *J. Amer. Chem. Soc.*, 1952, **74**, 1485; Biel, Drukker, Friedman, Horner, Leiser, and Sprengler, *ibid.*, 1955, **77**, 2250; Feldkamp, Faust, and Cushman, *ibid.*, 1952, **74**, 3831; Lands, *J. Pharmacol.*, 1951, **102**, 210.
[3] Blicke, U.S.P. 2,695,301/1954; Blicke and Lu, *J. Amer. Chem. Soc.*, 1955, **77**, 29.
[4] Oddo, *Gazzetta*, 1912, **42**, 257.
[5] Maxim, Zugravescu, and Fulga, *Bull. Soc. chim. France*, 1938, **5**, 44.
[6] Ryskiewicz and Silverstein, *J. Amer. Chem. Soc.*, 1954, **76**, 5802; *J. Org. Chem.* 1955, **20**, 668.
[7] Renshaw and Cass, *J. Amer. Chem. Soc.*, 1939, **61**, 1195.
[8] Signaigo and Adkins, *ibid.*, 1936, **58**, 1122.
[9] Dannley, Lukin, and Shapiro, *J. Org. Chem.*, 1955, **20**, 92.
[10] Cf. Karrer and Portman, *Helv. Chim. Acta*, 1948, **31**, 2088.
[11] Hess, Merck, and Ulbrig, *Ber.*, 1915, **48**, 1886.

XUM

of the starting material 2-(2-hydroxyethyl)pyrrole (by the action of ethylene oxide on pyrrylmagnesium bromide), as well as in its subsequent hydrogenation, an alternative route utilising the more readily available ethyl α-(1-methyl-2-pyrryl)acetate [12] was adopted. Hydrogenation of this ester in acetic acid at room temperature under pressure gave ethyl α-(1-methyl-2-pyrrolidinyl)acetate, which on reduction with lithium aluminium hydride gave 2-(2-hydroxyethyl)-1-methylpyrrolidine (V; $R^1 = H$, $R^2 = Me$; $n = 2$).



1-Ethyl-2-(2-hydroxyethyl)pyrrolidine (V; $R^1 = H$, $R^2 = Et$, $n = 2$), 1-*n*-propyl-2-(2-hydroxyethyl)-1-*n*-propylpyrrolidine (V; $R^1 = H$, $R^2 = Pr$; $n = 2$), and 2-(2-hydroxyethyl)-1 : 5-dimethylpyrrolidine (V; $R^1 = R^2 = Me$; $n = 2$) were obtained by analogous reactions. 1-Benzyl-2-(2-hydroxyethyl)pyrrolidine (V; $R^1 = H$, $R^2 = CH_2Ph$; $n = 2$) was obtained by reduction, with lithium aluminium hydride, of ethyl α-(1-benzyl-2-pyrrolidinyl)acetate which was itself obtained by the action of benzyl bromide on ethyl 2-pyrrolidinylacetate.[13] The same alcohol (V; $R^1 = H$, $R^2 = CH_2Ph$; $n = 2$) was prepared by Baker, Schaub, and Williams [14] by similar reduction of ethyl α-(1-benzyl-5-oxo-Δ^2-pyrrolinyl)acetate.

2-(3-Hydroxypropyl)-1-methylpyrrolidine (V; $R^1 = H$, $R^2 = Me$; $n = 3$) has been prepared by two routes. In the first methyl β-(5-oxo-2-pyrrolidinyl)propionate (VII) was prepared from dimethyl γ-nitropimelate by the method of Leonard *et al.*[15] Reduction with lithium aluminium hydride gave 2-(3-hydroxypropyl)pyrrolidine (V; $R^1 = R^2 = H$; $n = 3$) which on methylation with formaldehyde and formic acid then gave the desired alcohol (V; $R^1 = H$, $R^2 = Me$; $n = 3$). The second route utilised the condensation of 2-formyl-1-methylpyrrole with diethyl malonate to give the ester (VIII; R = Et) which was readily hydrolysed to the dicarboxylic acid (VIII; R = H). Since attempts to decarboxylate this acid failed, the diester was hydrogenated under pressure at room temperature in acetic acid (platinic oxide catalyst) to the reduced ester (IX) which on hydrolysis with alcoholic potassium hydroxide solution (0·5 equiv.) was converted into ethyl β-(1-methyl-2-pyrrolidinyl)propionate (X). Reduction with lithium aluminium hydride then gave the desired alcohol (V; $R^1 = H$, $R^2 = Me$; $n = 3$).

Esters of diphenylacetic, fluorene-9-carboxylic, and xanthen-9-carboxylic acid incorporating the *N*-alkyl-2-pyrrolidinylalkanol were prepared by conventional treatment of the acid chlorides with the alkanol in benzene, chloroform, or ether. Esters of benzilic acid were prepared by King and Holmes's method [16] in which benzilic acid was converted by phosphorus pentachloride into α-chlorodiphenylacetyl chloride which was then allowed to react with the basic alkanol, the resulting α-chlorodiphenylacetate hydrochloride, which was sometimes isolated, being hydrolysed with water to the diphenylglycollate hydrochloride. This was then either isolated directly or converted into the free base, and the hydrochloride was prepared from this as a separate experiment. Quaternary salts of the basic esters were prepared and isolated by the usual techniques.

The diphenylglycollate, its hydrochloride, and its methiodide prepared from the

[12] Sohl and Shriner, *J. Amer. Chem. Soc.*, 1933, **55**, 3828; Nenitzescu and Solomonica, *Ber.*, 1931, **64**, 1924.
[13] Clemo and Melrose, *J.*, 1942, 424.
[14] Baker, Schaub, and Williams, *J. Org. Chem.*, 1952, **17**, 117.
[15] Leonard, Hruda, and Long, *J. Amer. Chem. Soc.*, 1947, **69**, 690.
[16] King and Holmes, *J.*, 1947, 164.

2-hydroxymethyl-1-methylpyrrolidine derived from L-glutamic acid did not depress the melting points of the corresponding compounds prepared from the racemic form of the alcohol, although the melting points differed by several degrees. Blicke and Lu [3] obtained a diphenylglycollate hydrochloride by the reaction of 2-chloromethyl-1-methylpyrrolidine with benzilic acid in propan-2-ol, but give a melting point lower than that observed by us.

The pharmacological properties of the ester hydrochlorides and their quaternary salts have been investigated by Mr. D. M. Brown of these Laboratories and the results, which demonstrate the high antispasmodic activity of some of the benzilic acid esters, have been published.[17]

Experimental

Pyrrole-2-carboxylic Acid.—The following modification of Oddo's method [4] gave reproducible results: Freshly distilled pyrrole (99 g.) was added to a boiling solution of the Grignard reagent from magnesium turnings (34 g.) and ethyl bromide (157 g.) in ether (450 ml.), during 0·5 hr. with stirring. The mixture was then refluxed for 2 hr. and poured with stirring on a large excess of powdered solid carbon dioxide. After evaporation of excess of carbon dioxide the residue was acidified with 5N-sulphuric acid and filtered. The ether layer was separated and the aqueous layer extracted with ether (4 × 100 ml.). The combined ether layers were washed with water (3 × 75 ml.), dried ($MgSO_4$), and evaporated. The unchanged pyrrole (32 g.) was removed at 100° (bath)/3 mm., and the residual solid then dissolved in aqueous ammonia solution (*d* 0·88) and extracted with ether. This ether extract was rejected and the ammonia solution on acidification with concentrated hydrochloric acid gave pyrrole-2-carboxylic acid (53 g., 47%), m. p. 180—181°, sufficiently pure for esterification.

The acid (11 g.) in dry methanol (140 ml.) with diazomethane [400 ml. from nitrosomethylurea (40 g.)] gave the pale yellow methyl ester (10 g., 74%), m. p. 70—72° (Blicke and Blake [18] give m. p. 73°).

Methyl 1-Methylpyrrole-2-carboxylate.—A solution of methyl pyrrole-2-carboxylate (21 g.) in dry toluene (25 ml.) was added during 0·5 hr. to a boiling, stirred suspension of " molecular potassium " (6·5 g.) in dry toluene (150 ml.). After refluxing for 23 hr. the solvent was removed under reduced pressure and the residual solid refluxed, with stirring, with excess of methyl iodide (101 ml.) for 36 hr. The inorganic material was collected and washed with dry ether. After evaporation of the filtrate the residual liquid, on distillation *in vacuo*, gave *methyl 1-methylpyrrole-2-carboxylate* (28 g., 77%), b. p. 62°/1 mm., $n_D^{16\cdot5}$ 1·5222 (Found: C, 60·7; H, 6·5; N, 10·2. $C_7H_9O_2N$ requires C, 60·4; H, 6·5; N, 10·1%).

2-Hydroxymethyl-1-methylpyrrole.—The preceding ester (37 g.) in dry ether (*ca.* 150 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (10 g.) in dry ether (300 ml.) during 0·5 hr. (gentle ebullition). The mixture was then refluxed for 2·5 hr. and thereafter cooled. Ice-cold water (35 ml.) was cautiously added, the solution filtered, and the inorganic residue washed with ether. The combined washings and the filtrate were dried ($MgSO_4$) and evaporated and the residual liquid was distilled *in vacuo* to give 2-hydroxymethyl-1-methylpyrrole (23 g., 87%), b. p. 82°/2 mm., $n_D^{15\cdot5}$ 1·5308 (Found: C, 65·0; H, 8·4; N, 12·0. Calc. for C_6H_9ON: C, 64·9; H, 8·1; N, 12·6%). The product dissolved in acetic acid to a deep yellow solution, from which a yellow solid began to separate. This quickly became red and a rapid exothermic polymerisation resulted in a violent explosion.

Diethyl Pyrrolidine-1 : 2-dicarboxylate.—Diethyl pyrrole-1 : 2-dicarboxylate [8] (30 g.) in glacial acetic acid (75 ml.) was hydrogenated at an initial pressure of 100 atm. in the presence of platinic oxide (3 g.) at room temperature for 2 hr.: up-take (6 atm.) of hydrogen was by then complete. The catalyst was removed and the acetic acid neutralised with saturated aqueous potassium carbonate. Potassium acetate separated and sufficient anhydrous potassium carbonate (66 g.) was added to saturate the aqueous layer. The inorganic material was collected and washed with ether (4 × 50 ml.). The ether was separated from the filtrate, and the aqueous layer was further extracted with ether (4 × 250 ml.). The combined ether extracts were dried ($MgSO_4$) and evaporated and the residual oil distilled *in vacuo* to give diethyl pyrrolidine-1 : 2-dicarboxylate (25 g., 83%), b. p. 131—133°/4 mm., n_D^{23} 1·4545 (Signaigo and Adkins [8] give b. p. 133—134°/8 mm., n_D^{25} 1·4530).

[17] Acred, Atkins, Bainbridge, Brown, Quinton, and Turner, *Brit. J. Pharmacol.*, 1957, **12**, 447.
[18] Blicke and Blake, *J. Amer. Chem. Soc.*, 1930, **52**, 235.

Butyl 5-Oxopyrrolidine-2-carboxylate.—This was prepared by esterification of L-glutamic acid (Segel's procedure [19]) in 55—65% yield and had b. p. 180°/6·5 mm., $n_D^{19·5}$ 1·4739 (Found: C, 58·2; H, 8·1; N, 8·0. Calc. for $C_9H_{15}O_3N$: C, 58·4; H, 8·1; N, 7·6%) (lit.;[10] yield 65%; b. p. 157—160°/1·3 mm.).

2-Hydroxymethylpyrrolidine.—The foregoing butyl ester (80 g.) in ether (3·5 l.) was reduced with lithium aluminium hydride (40 g.) in dry ether (3·5 l.). The mixture was refluxed for 18—22 hr. and then worked up as described previously to give after careful fractionation 2-hydroxymethylpyrrolidine (67%), b. p. 89°/6 mm., n_D^{20} 1·4846 (Found: C, 59·2; H, 10·7. Calc. for $C_5H_{11}ON$: C, 59·4; H, 10·9%). Its *picrate*, prepared in ether, crystallised from ethyl acetate–ether as prisms, m. p. 106—107° (Found: C, 40·2; H, 4·4; N, 17·2. $C_{11}H_{14}O_8N_4$ requires C, 40·0; H, 4·2; N, 17·0%).

2-Hydroxymethyl-1-methylpyrrolidine.—(*a*) 2-Hydroxymethylpyrrolidine (50 g.) was added with cooling to anhydrous formic acid (95 ml., *d* 1·2), followed by 40% aqueous formaldehyde (65 ml.). When the initial vigorous evolution of carbon dioxide had subsided, the whole was refluxed for 16—20 hr., cooled, acidified with 5N-hydrochloric acid (230 ml.), and evaporated *in vacuo* to dryness, a dark gum being obtained which on cooling set to needles. These were dissolved in a minimum quantity of water (*ca.* 150 ml.), saturated with sodium hydroxide, and extracted with chloroform (7 × 50 ml.). The combined extracts were dried (K_2CO_3), the chloroform removed at 400 mm., and the residual oil distilled *in vacuo*. The fraction, b. p. 49—50°/2 mm., on redistillation gave 2-hydroxymethyl-1-methylpyrrolidine (35 g., 61%), b. p. 57°/4 mm., $n_D^{19·5}$ 1·4692 (Found: C, 62·1; H, 11·1. Calc. for $C_6H_{13}ON$: C, 62·6; H, 11·3%). Blicke and Lu [3] give b. p. 67—69°/12 mm.

(*b*) Diethyl pyrrolidine-1 : 2-dicarboxylate (25 g.) in ether (1 l.) was reduced by dropwise addition during 0·5 hr. to a stirred suspension of lithium aluminium hydride (9 g.) in dry ether (2 l.). The mixture was refluxed for 22 hr. and then worked up as described previously to give 2-hydroxymethyl-1-methylpyrrolidine (9 g., 65%), b. p. 68—70°/14 mm., n_D^{23} 1·4678 (Renshaw and Cass [7] report b. p. 77°/15 mm.). The picrate, prepared in ether, crystallised from ethanol as needles, m. p. 173—174° (lit.,[7] m. p. 173°).

1 : 2-Dimethylpyrrole.—This was obtained by Rapoport and Jorgensen's method.[20] It was also obtained as follows by Wolff–Kishner reduction of 2-formyl-1-methylpyrrole (cf. King and Nord [21]). 2-Formyl-1-methylpyrrole (23 g.), ethylene glycol (170 ml.), and 60% aqueous hydrazine hydrate (63 ml.) were heated in a bath to 160° (internal temperature) and the water removed by distillation. The whole was then allowed to cool to 60° and potassium hydroxide (pellets) (42 g.) added. Heating was then continued at an internal temperature of 130° for 1 hr. until nitrogen ceased to be evolved. After cooling, the mixture was extracted with ether (6 × 50 ml.), the ether extracts were dried (KOH) and evaporated, and the residual oil (10 g., 48%) was distilled, to give 1 : 2-dimethylpyrrole, b. p. 138°, n_D^{27} 1·4898 (Rapoport and Jorgensen [20] give b. p. 139—140°, n_D^{25} 1·4913).

α-(*1-Alkyl-2-pyrryl*)*acetates.*—These were obtained following the general method described by Sohl and Shriner [12] for ethyl 1-methyl-2-pyrrylacetate: Ethyl 1-ethyl-2-pyrrylacetate (41%), b. p. 102—110°/3 mm. Ethyl 1-*n*-propyl-2-pyrrylacetate (36%), b. p. 79—87°/0·05 mm., n_D^{24} 1·4847. *Ethyl* 1 : 2-*dimethyl-5-pyrrylacetate* (71%), b. p. 98°/1 mm., n_D^{16} 1·4950 (Found: C, 66·0; H, 8·5; N, 8·3. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3; N, 7·7%).

α-(*1-Substituted 2-pyrrolidinyl*)*acetates.*—These were obtained by the following modification of Sohl and Shriner's method: [12]

Ethyl 1-methyl-2-pyrrolidinylacetate. Hydrogenation of ethyl 1-methyl-2-pyrrylacetate in glacial acetic acid at 100 atm. for 16 hr. at room temperature in the presence of platinic oxide gave ethyl 1-methyl-2-pyrrolidinylacetate (65%), b. p. 65—66°/2·5 mm., $n_D^{18·5}$ 1·4464 (Found: C, 63·1; H, 9·8; N, 8·4. Calc. for $C_9H_{17}O_2N$: C, 63·2; H, 9·9; N, 8·2%) (Sohl and Shriner [12] report b. p. 88—89°/10 mm., n_D^{20} 1·4465).

Similarly were prepared:

Ethyl 1-ethyl-2-pyrrolidinylacetate (75%), b. p. 83—84°/4 mm., n_D^{20} 1·4487 (Found: C, 64·5; H, 10·6; N, 7·3. $C_{10}H_{19}O_2N$ requires C, 64·9; H, 10·3; N, 7·6%).

Ethyl 1-n-*propyl-2-pyrrolidinylacetate* (41%), b. p. 99°/4·5 mm., n_D^{23} 1·4488 (Found: C, 66·2; H, 10·5; N, 7·4. $C_{11}H_{21}O_2N$ requires C, 66·3; H, 10·6; N, 7·0%) [*hydrochloride* crystallised

[19] Segel, *J. Amer. Chem. Soc.*, 1952, **74**, 852.
[20] Rapoport and Jorgensen, *J. Org. Chem.*, 1949, **14**, 664.
[21] King and Nord, *ibid.*, 1949, **14**, 641.

from ethyl acetate–methanol–ether as prisms, m. p. 130—131° (Found: C, 55·9; H, 9·3; N, 5·9. $C_{11}H_{22}O_2NCl$ requires C, 56·1; H, 9·3; N, 5·9%)].

Ethyl **1** : 2-*dimethyl*-5-*pyrrolidinylacetate* (73%), b. p. 71°/1·5 mm., n_D^{20} 1·4462 (C, 64·2; H, 10·2; N, 7·8. $C_{10}H_{19}O_2N$ requires C, 64·9; H, 10·3; N, 7·6%) {*picrate* [from ethyl acetate–light petroleum (b. p. 40—60°)], needles, m. p. 119° (Found: C, 46·7; H, 5·5; N, 13·7. $C_{16}H_{22}O_9N_4$ requires C, 46·3; H, 5·3; N, 13·6%)}.

Ethyl 1-*Benzyl*-2-*pyrrolidinylacetate*.—Ethyl 2-pyrrolidinylacetate [13] (24 g.), anhydrous potassium carbonate (16 g.), and benzyl bromide (26 g.) in dry toluene (150 ml.) were refluxed for 1·5 hr. and then filtered. The inorganic residue was extracted with boiling toluene (*ca.* 30 ml.), and the combined toluene filtrates were evaporated. The residual liquid on distillation *in vacuo* gave *ethyl* 1-*benzyl*-2-*pyrrolidinylacetate* (25 g., 66%), b. p. 108°/0·02 mm., $n_D^{21\cdot5}$ 1·5095 (Found: C, 72·9; H, 8·4; N, 5·9. $C_{15}H_{21}O_2N$ requires C, 72·9; H, 8·5; N, 5·7%). [*Picrate*, needles (from ethyl acetate–ether), m. p. 99—100° (Found: C, 53·2; H, 5·2; N, 11·9. $C_{21}H_{24}O_9N_4$ requires C, 53·0; H, 5·0; N, 11·8%).]

1-*Substituted* 2-(2-*Hydroxyethyl*)*pyrrolidines*.—The following were obtained by reduction of the corresponding esters in ether with lithium aluminium hydride in the usual manner:

2-(2-Hydroxyethyl)-1-methylpyrrolidene (65%), b. p. 77°/3·5 mm., n_D^{18} 1·4726 (Found: C, 64·7; H, 11·2; N, 11·2. Calc. for $C_7H_{15}ON$: C, 65·1; H, 11·6; N, 10·9%) (Hess *et al.*[11] give b. p. 110—120°/14 mm.). The *tri-iodophenylurethane*, prepared in light petroleum (b. p. 60—80°), crystallised from light petroleum (b. p. 110—120°)–chloroform (trace) as needles, m. p. 173—174° (decomp.) (Found: C, 27·2; H, 2·9. $C_{14}H_{17}O_2N_2I_3$ requires C, 26·8; H, 2·7%).

1-*Ethyl*-2-(2-*hydroxyethyl*)*pyrrolidine* (77%), b. p. 95°/3·5 mm., n_D^{20} 1·4742 (Found: C, 66·5; H, 11·9; N, 9·9. $C_8H_{17}ON$ requires C, 67·1; H, 11·9; N, 9·8%).

2-(2-*Hydroxyethyl*)-1-n-*propylpyrrolidine* (75%), b. p. 91°/1 mm., n_D^{24} 1·4685 (Found: N, 9·2. $C_9H_{19}ON$ requires N, 8·9%). The *tri-iodophenylurethane*, prepared in light petroleum (b. p. 60—80°), crystallised from light petroleum (b. p. 80—100°) as prisms, m. p. 79—80° (Found: C, 28·9; H, 3·3; N, 4·2. $C_{16}H_{21}O_2N_2I_3$ requires C, 29·4; H, 3·2; N, 4·3%).

5-(2-Hydroxyethyl)-1 : 2-dimethylpyrrolidine (78%), b. p. 68—72°/1·5 mm., n_D^{19} 1·4795 (analysis was unsatisfactory).

1-*Benzyl*-2-(2-*hydroxyethyl*)*pyrrolidine* (79%), b. p. 110°/0·05 mm., n_D^{24} 1·5370 (Found: C, 75·3; H, 9·6; N, 6·5. Calc. for $C_{13}H_{19}ON$: C, 76·1; H, 9·3; N, 6·8%) (Baker *et al.*[14] give b. p. 112—115°/0·05 mm.). The *picrate* crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as needles, m. p. 78—79° (Found: C, 52·5; H, 5·0; N, 13·3. $C_{19}H_{22}O_8N_4$ requires C, 52·5; H, 5·1; N, 12·9%).

2-(3-*Hydroxypropyl*)*pyrrolidine*.—A solution of methyl β-(5-oxo-2-pyrrolidinyl)propionate [15] (22 g.) in dry tetrahydrofuran (110 ml.) was added dropwise to a suspension of lithium aluminium hydride (15 g.) in dry ether (250 ml.) and tetrahydrofuran (110 ml.). Isolation in the usual manner gave 2-(3-*hydroxypropyl*)*pyrrolidine* (5 g., 31%), b. p. 118°/4·5 mm., m. p. *ca.* 30° (Found: C, 64·6; H, 11·7; N, 11·0. $C_7H_{15}ON$ requires C, 65·1; H, 11·6; N, 10·9%).

Ethyl α-*Ethoxycarbonyl*-β-(1-*methyl*-2-*pyrryl*)*acrylate*.—2-Formyl-1-methylpyrrole [6] (100 g.), diethyl malonate (155 ml.), ethanol (920 ml.), and piperidine (64 ml.) were refluxed for 4 hr. A part of the solvent (*ca.* 500 ml.) was evaporated and the residual solution cooled to give pale pink crystals which were filtered off and washed with a small amount of light petroleum (b. p. 80—100°)–ethanol (3 : 1), to give crystals (76 g.), m. p. 72°. The combined washings and the filtrate were further evaporated to give an oil which crystallised to a second crop of crystals (86·5 g.), m. p. 71°. Repetition of this procedure gave a further crop of crystals (13·5 g.), m. p. 68—69°, the total yield of *ethyl* α-*ethoxycarbonyl*-β-(1-*methyl*-2-*pyrryl*)*acrylate* being 176 g. (76%). Crystallisation from light petroleum (b. p. 80—100°)–ethanol (3 : 1) gave prisms, m. p. 73° (Found: C, 62·0; H, 6·5; N, 5·7. $C_{13}H_{17}O_4N$ requires C, 62·2; H, 6·8; N, 5·6%).

α-*Carboxy*-β-(1-*methyl*-2-*pyrryl*)*acrylic Acid*.—The above ester (5 g.) was warmed with potassium hydroxide (4·3 g.) in water (15 ml.) to give complete solution, which was then refluxed for 0·25 hr. Evaporation to half volume *in vacuo*, followed by ether-extraction (3 × 10 ml.), gave an aqueous layer which was acidified with concentrated hydrochloric acid (8 ml.). The separated solid (3 g., 81%) was filtered off and crystallised from acetone–light petroleum (b. p. 60—80°) to give α-*carboxy*-β-(1-*methyl*-2-*pyrryl*)*acrylic acid* as yellow prisms, m. p. 167° (Found: C, 55·4; H, 4·8; N, 7·5. $C_9H_9O_4N$ requires C, 55·3; H, 4·6; N, 7·2%).

XUM

Ethyl α-Ethoxycarbonyl-β-(1-methyl-2-pyrrolidinyl)propionate.—Ethyl α-ethoxycarbonyl-β-(1-methyl-2 pyrryl)acrylate (64 g.) in glacial acetic acid (250 ml.) was hydrogenated at room temperature at an initial pressure of 100 atm. in the presence of platinic oxide (5 g.). After being stirred for 16 hr. the mixture was worked up as previously described. A fraction (58 g.,

Esters, etc., $Ph_2C(OH)\cdot CO\cdot O\cdot[CH_2]_n$–(N-R)

No.	*n*	R	Salt	Yield (%) †	M. p.	Form and solvent ‡
1	1	Me	—	53	100—101°,[a] 104°[b]	Needles, Pet
2	1	Me	HCl	61	* 170—171,[a] 182—183[b]	Needles, COMeEt
				67		
3	1	Me	MeI	97	192,[a] 184[b]	Prisms, EtOAc–MeOH–Et_2O
				84		
4	1	Me	MeBr	—	171[a]	Needles, $COMe_2$
5	1	Me	Me_2SO_4	84	154—155[a]	Needles, COMeEt–EtOH–Et_2O
6	1	Me	EtI	40	148—150[a]	Needles, EtOAc–MeOH–Et_2O
7	2	H[d]	—	38	125	Needles, Pet
8	2	H	HCl	—	143—144	Needles, EtOH–Et_2O
9	2	Me	—	56	82—83	Needles, Pet
10	2	Me	HCl	58	134	Prisms, EtOH–Et_2O
11	2	Me	MeI	66	153	Needles, EtOH–Et_2O
12	2	Me	MeBr	78	148—149	Needles, COMeEt–Et_2O
13	2	Me	EtI	56	176—177	Prisms, COMeEt–EtOH
14	2	Me	*n*-PrI	71	178	Needles, COMeEt–EtOH
15	2	Et	HCl	89	151	Prisms, EtOH–Et_2O
16	2	Et	EtI	80	162	Needles, COMeEt–EtOH
17	2	*n*-Pr	—	42	B. p. 156—157°/5 × 10^{-4} mm., n_D^{23} 1·5491	—
18	2	*n*-Pr	HCl	—	149—150	Needles, EtOAc–MeOH–Et_2O
19	3	Me	—	88	84	Needles, Pet
20	3	Me	HCl	—	122	Needles, COMeEt–Pet
21	3	Me	MeI	85	130	Needles, EtOAc–EtOH

No.	Formula	Found (%) C	H	N	Hal	Required (%) C	H	N	Hal
1	$C_{20}H_{23}O_3N$	73·9	7·2	4·3	—[a]	73·8	7·1	4·3	—
		73·6	7·2	4·1	—[b]				
2	$C_{20}H_{24}O_3NCl$	66·4	6·7	4·3	9·9[a]	66·4	6·6	3·9	9·8
		66·2	6·7	4·1	10·0[b]				
3	$C_{21}H_{26}O_3NI$	53·8	5·7	—	26·8[a]	54·0	5·6	—	27·2
		54·2	5·8	—	27·2[b]				
4	$C_{21}H_{26}O_3NBr$	60·5	6·6	—	19·4	60·0	6·2	—	19·0
5	$C_{22}H_{29}O_7NS$	58·9	6·5	—	6·9[c]	58·5	6·4	—	7·1[c]
6	$C_{22}H_{28}O_3NI$	54·7	5·6	—	26·0	54·9	5·8	—	26·4
7	$C_{20}H_{23}O_3N$	74·1	7·2	4·4	—	73·8	7·1	4·3	—
8	$C_{20}H_{24}O_3NCl$	66·5	7·0	—	9·3	66·4	6·6	—	9·8
9	$C_{21}H_{25}O_3N$	74·3	7·2	4·2	—	74·4	7·4	4·1	—
10	$C_{21}H_{26}O_3NCl$	66·9	6·8	4·0	—	67·1	6·9	3·7	—
11	$C_{22}H_{28}O_3NI$	55·0	5·9	2·3	—	54·9	5·8	2·9	—
12	$C_{22}H_{28}O_3NBr$	60·6	6·4	3·3	—	60·8	6·5	3·2	—
13	$C_{22}H_{30}O_3NI$	55·8	6·0	3·2	—	55·7	6·1	2·8	—
14	$C_{24}H_{32}O_3NI$	55·8	6·2	—	—	56·7	6·3	—	—
15	$C_{22}H_{30}O_3NCl$	68·1	7·3	3·8	—	67·8	7·2	3·6	—
16	$C_{24}H_{32}O_3NI$	56·6	6·5	—	24·7	56·6	6·3	—	24·9
17	$C_{23}H_{29}O_3N$	75·2	8·0	4·1	—	75·2	7·9	3·8	—
18	$C_{23}H_{30}O_3NCl$	68·1	7·3	—	8·7	68·4	7·4	—	8·8
19	$C_{23}H_{27}O_3N$	74·9	7·8	4·3	—	74·8	7·7	4·0	—
20	$C_{22}H_{28}O_3NCl$	67·6	7·1	—	9·4	67·8	7·2	—	9·1
21	$C_{23}H_{30}O_3NI$	55·4	6·2	—	25·9	55·8	6·1	—	25·7

[a] Product obtained from 2-hydroxymethyl-1-methylpyrrolidine derived from L-glutamic acid. [b] Product obtained from 2-hydroxymethyl-1-methylpyrrolidine derived from diethyl pyrrolidine-1 : 2-dicarboxylate. [c] Analysis for sulphur. [d] Prepared by the hydrogenation of 1-benzyl-2-[2-(αα-diphenylglycolloyloxy)ethyl]pyrrolidine (crude) in acetic acid at an initial pressure of 66 lb./sq. in. with 10% palladium–charcoal. The benzilic ester was prepared, by the described general method, from 1-benzyl-2-(2-hydroxyethyl)pyrrolidine.

* Blicke and Lu [3] give m. p. 161—162°. † Yields of hydrochlorides given only where they were isolated directly from the reaction mixture. ‡ Pet = light petroleum.

XUM

88%) of b. p. 93—100°/0·5 mm. was collected, which on redistillation gave *ethyl α-ethoxycarbonyl-β-(1-methyl-2-pyrrolidinyl)propionate*, b. p. 88°/0·1 mm., n_D^{21} 1·4524 (Found: C, 60·8; H, 9·2; N, 5·5. $C_{13}H_{23}O_4N$ requires C, 60·8; H, 9·0; N, 5·5%).

Ethyl β-(1-Methyl-2-pyrrolidinyl)propionate.—Ethanolic 1·25N-potassium hydroxide (125 ml., 1 equiv.) was added to a solution of the above ester (40 g., 2 equiv.) in ethanol (40 ml.). After 16 hr. at room temperature the solvent was removed *in vacuo* and 1·18N-hydrochloric acid (132 ml.) was added. The mixture was evaporated to dryness *in vacuo*, ethanol (50 ml.) added, and the mixture again evaporated to dryness to ensure complete removal of water. Dry ethanol (50 ml.) was added to the residue, the ethanolic solution filtered, and the inorganic material (2·7 g.) washed with dry ethanol (25 ml.). Evaporation of the filtrate followed by distillation of the residue gave a fraction (23 g., 79%) of b. p. 48—50°/0·05 mm. which on redistillation gave *ethyl β-(1-methyl-2-pyrrolidinyl)propionate*, b. p. 48°/0·04 mm., n_D^{23} 1·4520 (Found: C, 64·9; H, 10·5; N, 7·9. $C_{10}H_{19}O_2N$ requires C, 64·8; H, 10·3; N, 7·6%). Its *picrate*, prepared in ethyl acetate, crystallised from ethyl acetate–light petroleum (b. p. 40—60°) as needles, m. p. 106° (Found: C, 46·1; H, 5·3; N, 13·4. $C_{16}H_{22}O_9N_4$ requires C, 46·4; H, 5·3; N, 13·5%).

2-(3-*Hydroxypropyl*)-1-*methylpyrrolidine.*—(*a*) Reduction of ethyl β-(1-methyl-2-pyrrolidinyl)propionate (28 g.) in dry ether (300 ml.) with lithium aluminium hydride (6 g.) gave 2-(3-*hydroxypropyl*)-1-*methylpyrrolidine* (18 g., 86%), b. p. 60°/0·03 mm., n_D^{20} 1·4741 (Found: C, 67·0; H, 12·2; N, 9·6. $C_8H_{17}ON$ requires C, 67·1; H, 11·9; N, 9·8%) [*picrate*, needles, m. p. 53°, from chloroform–*cyclo*hexane (Found: N, 15·3. $C_{14}H_{20}O_8N_4$ requires C, 45·2; H, 5·4; N, 15·0%)].

(*b*) 2-(3-Hydroxypropyl)pyrrolidine (8 g.) was methylated with 90% formic acid (13·5 ml.) and 40% aqueous formaldehyde (7 ml.) as previously described. 2-(3-Hydroxypropyl)-1-methylpyrrolidine (5 g., 60%) was obtained as a liquid, b. p. 103—104°/2·5 mm., n_D^{21} 1·4720 [picrate, m. p. and mixed m. p. 54° (Found: C, 45·2; H, 5·7; N, 14·7%)].

2-[2-(αα-*Diphenylacetoxy*)*ethyl*]-1-*methylpyrrolidine.*—Reaction of 2-(2-hydroxyethyl)-1-methylpyrrolidine (7 g.) with diphenylacetyl chloride (13 g.) in benzene (60 ml.) at room temperature for 18 hr. gave a crude ester hydrochloride (13 g., 65%) which on basification with 30% aqueous potassium hydroxide gave 2-[2-(αα-*diphenylacetoxy*)*ethyl*]-1-*methylpyrrolidine* (9 g., 48%) as an amber oil, b. p. 165°/0·05 mm., n_D^{23} 1·5521 (Found: C, 77·8; H, 7·7; N, 4·3. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·7; N, 4·3%).

2-[2-(αα-*Diphenylacetoxy*)*ethyl*]-1-*ethylpyrrolidine* was prepared similarly from 1-ethyl-2-(2-hydroxyethyl)pyrrolidine as an amber viscous oil (55%), b. p. 168°/0·03 mm., $n_D^{19·5}$ 1·5511 (Found: C, 78·1; H, 8·0; N, 4·3. $C_{22}H_{27}O_2N$ requires C, 78·4; H, 8·0; N, 4·2%).

2-[2-(αα-*Diphenylacetoxy*)*ethyl*]-1 : 1-*dimethylpyrrolidinium Iodide.*—2-[2-(αα-Diphenylacetoxy)ethyl]-1-methylpyrrolidine (2 g.) was treated with methyl iodide (1·5 ml.) in toluene (25 ml.) for 18 hr. at room temperature. Crystallisation from butanone gave the *iodide* as pale yellow needles (2 g., 80%), m. p. 143—144° (Found: C, 56·5; H, 6·3; N, 2·7. $C_{22}H_{28}O_2NI$ requires C, 56·8; H, 6·0; N, 3·0%).

2-[2-(*Fluorene-9-carbonyloxy*)*ethyl*]-1-*methylpyrrolidine Hydrochloride.*—2-(2-Hydroxyethyl)-1-methylpyrrolidine (5 g.) with fluorene-9-carbonyl chloride (9 g.) in chloroform (80 ml.) at room temperature for 0·5 hr. gave the *ester hydrochloride* (4 g., 25%) as prisms, m. p. 164° (decomp.) (from ethanol–ether) (Found: C, 69·9; H, 6·6; N, 3·9. $C_{21}H_{24}O_2NCl$ requires C, 70·5; H, 6·7; N, 3·9%).

2-[2-(*Xanthen-9-carbonyloxy*)*ethyl*]-1-*methylpyrrolidine Hydrochloride.*—2-(2-Hydroxyethyl)-1-methylpyrrolidine (2·5 g.) with xanthen-9-carbonyl chloride (4·5 g.) in dry ether (400 ml.) for 18 hr. at room temperature gave a solid (5 g., 80%) which on crystallisation from ethanol–ether gave the *ester hydrochloride*, m. p. 197—198° (decomp.), as needles (Found: C, 67·1; H, 6·5; N, 3·5. $C_{21}H_{24}O_3NCl$ requires C, 67·5; H, 6·4; N, 3·8%).

2-[2-(*Xanthen-9-carbonyloxy*)*ethyl*]-1 : 1-*dimethylpyrrolidinium Iodide.*—The free base (4 g.) [liberated from the preceding hydrochloride (5 g.)] was allowed to react with methyl iodide (3·3 ml.) in toluene (50 ml.) at room temperature to give the *iodide* (4·5 g., 69%) as rods, m. p. 165° (from ethanol) (Found: C, 54·8; H, 5·7; N, 3·1. $C_{22}H_{26}O_3NI$ requires C, 55·1; H, 5·4; N, 2·9%).

2-[2-(αα-*Diphenylglycolloyloxy*)*ethyl*]-1 : 5-*dimethylpyrrolidine Hydrochloride.*—A solution of 2-(2-hydroxyethyl)-1 : 5-dimethylpyrrolidine (5 g.) in dry ether (100 ml.) was added with stirring to a solution of α-chlorodiphenylacetyl chloride (10 g.) in dry ether (300 ml.) during

0·5 hr. After being kept overnight at room temperature, the ethereal layer was decanted. The residual gum on trituration with dry ethanol (*ca.* 20 ml.) solidified and was collected (4 g.). This hydrochloride (4 g.) was dissolved in water (80 ml.) and left at room temperature for 30 min. Sodium chloride (30 g.) was added and the solution extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and evaporated to a gum, which crystallised from propan-2-ol–ether (1 : 6) to give the *ester hydrochloride* (3 g., 24%) as rods, m. p. 179—180° (Found: C, 67·4; H, 7·4; N, 3·5. $C_{23}H_{28}O_3NCl$ requires C, 67·8; H, 7·2; N, 3·6%).

2-[2-(αα-*Diphenylglycolloyloxy*)*ethyl*]-1 : 1 : 5-*trimethylpyrrolidinium iodide* was obtained by the previous procedure (89% yield) as a gum which solidified on trituration with butanone and crystallisation from ethanol–butanone (1 : 4) as needles, m. p. 154—155° (Found: C, 55·6; H, 6·1; N, 3·4. $C_{23}H_{30}O_3NI$ requires C, 55·8; H, 6·1; N, 2·9%).

Other Esters and Salts.—The Table records other *compounds* prepared by analogous methods.

The authors thank the Directors of Beecham Research Laboratories Ltd., for permission to publish the paper and, in particular, Dr. D. O. Holland for his interest and encouragement, Sir Ian Heilbron, F.R.S., and Dr. A. H. Cook, F.R.S., for valuable suggestions, Mr. A. Twamley for help in the experimental work, and the Staff of the Micro-analytical Department.

Organic Department, Beecham Research Laboratories Ltd.,
Betchworth, Surrey.
C. L. Bencard Ltd., Minerva Road,
Park Royal, London, N.W.10.

[*Received, June 26th*, 1958.]

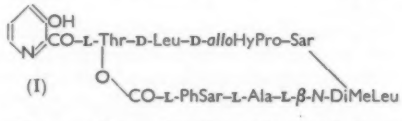
---

901. *The Structure of Viridogrisein (Etamycin).*

By R. B. Arnold, A. W. Johnson, and A. B. Mauger.

The results of degradative experiments support the structure (I) assigned recently to viridogrisein (etamycin) by Sheehan *et al.* The biogenesis of peptides containing macrocyclic lactone rings is discussed.

Viridogrisein [1] (etamycin [2]) is an antibiotic isolated from strains of *Streptomyces griseus* almost simultaneously in two American laboratories. Preliminary studies [2,3] of its hydrolysis showed it to be a peptide comprising 3-hydroxypicolinic acid and seven compounds giving colours with ninhydrin, including the amino-acids L-alanine, D-leucine, and D-*allo*hydroxyproline. Ingenious degradative studies by Sheehan and his co-workers [4] have recently revealed the total structure of viridogrisein as (I), a peptide which contains three *N*-methylamino-acids (sarcosine, L-phenylsarcosine, and L-β-*N*-dimethyl-leucine) and in which the hydroxyl group of L-threonine is esterified by the carboxyl group of the



(I)

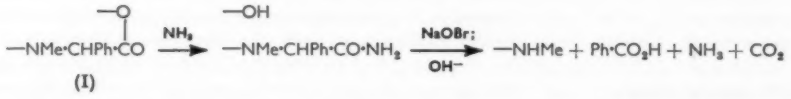
C-terminal amino-acid. The position of L-threonine and its participation in a macrolactone ring recalls the structure of the actinomycins,[5,6] and it is possible that pyridomycin [7] and echinomycin [8] (serine instead of threonine) may contain similar features.

Through the courtesy of Drs. R. E. Bowman and Q. Bartz of Parke Davis & Co., we

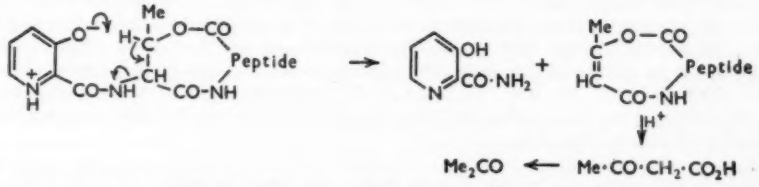
[1] Bartz, Standiford, Mold, Johannessen, Ryder, Maretzki, and Haskell, *Antibiotics Annual*, 1954—55, 777.
[2] Heinemann, Gourevitch, Lein, Johnson, Kaplan, Vanas, and Hooper, *ibid.*, p. 728.
[3] Haskell, Maretzki, and Bartz, *ibid.*, p. 784.
[4] Sheehan, Zachau, and Lawson, *J. Amer. Chem. Soc.*, 1957, **79**, 3933.
[5] Brockmann, Bohnsack, Franck, Gröne, Muxfeldt, and Süling, *Angew. Chem.*, 1956, **68**, 70.
[6] Bullock and Johnson, *J.*, 1957, 3280.
[7] Maeda, Kosaka, Okami, and Umezawa, *J. Antibiotics*, 1953, *A*, **6**, 140; Yagashita, *ibid.*, 1957, *A*, **10**, 5.
[8] Corbaz, Ettlinger, Gäumann, Keller-Schierlein, Kradolfer, Neipp, Prelog, Reusser, and Zähner, *Helv. Chim. Acta*, 1957, **40**, 199; Keller-Schierlein and Prelog, *ibid.*, p. 205.

have been able to examine a sample of viridogrisein, and the results of our degradative experiments, most of which were carried out before appearance of the communication of Sheehan *et al.*,[4] are in accord with his structure (I). The antibiotic has not yet been obtained crystalline, but it has been purified both by counter-current distribution [1] and through the crystalline hydrochloride.[2] In our experience, viridogrisein can be purified conveniently by precipitation of the colourless crystalline ammonium salt which separates rapidly from solutions of viridogrisein in ethanolic ammonia, leaving the impurities in solution. The salt is unstable in the dry state and by allowing the decomposition to proceed *in vacuo* the pure antibiotic can be obtained. The formation of the ammonium salt was somewhat unexpected in the absence of a carboxylic acid group but it has since been shown that both ethyl 3-hydroxypicolinate and 3-hydroxypicolinamide form similar unstable ammonium salts. The acidity of the phenolic function is evidently enhanced by the electron-attracting carbonyl group and the heterocyclic nitrogen atom in these compounds (pK_a of viridogrisein,[3] 7·3).

The evidence for the existence of the lactone ring lies in the infrared spectrum [3] (band at 1751 cm.$^{-1}$) and the observation that saponification at room temperature releases a carboxylic acid group in forming viridogriseic acid [3] (etamycin acid [4]). Further, whereas three of the products, L-threonine, D-*allo*hydroxyproline, and 3-hydroxypicolinic acid, obtained from the acid hydrolysis of viridogrisein, contain hydroxyl groups, we have found that viridogrisein itself yields a diacetate and consequently one of the hydroxyl groups which appears in the degradation products is either sterically hindered in the original antibiotic or is freed only on hydrolysis. The lactone ring can also be opened by ammonolysis, giving a *C*-terminal amide, and when this product was subjected to Hofmann degradation, followed by acid hydrolysis, it gave a small yield of benzoic acid. This confirms the view that the aromatic phenylsarcosine is the *C*-terminal unit of the peptide, the course of the degradation being visualised as follows:



Pyrolysis of viridogrisein alone at 220° or in pyridine at 160° gives 3-hydroxypicolinamide, which can be sublimed from the reaction mixture. For comparison with the degradation product, 3-hydroxypicolinamide was obtained from the corresponding acid [9] by esterification and ammonolysis. The pyrolysis is interpreted as an olefin-forming elimination, especially as acetone can be isolated by vigorous hydrolysis of the pyrolysis residue. The acetone arises from the peptide threonyl grouping which is converted into an acetoacetic acid enol residue as a result of the amide elimination. This observation is confirmatory evidence that 3-hydroxypicolinic acid is attached to threonine and it reveals the amide character of the linkage. As spectroscopic and dipole-moment measurements [10] indicate the presence of dipolar forms in 3-hydroxypyridine, a plausible reaction mechanism for this decomposition can be postulated:



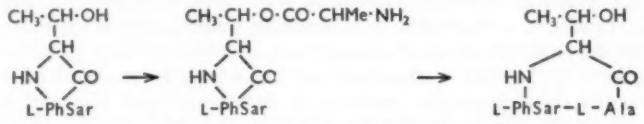
Mycobactin, which gives 2-hydroxy-6-methylbenzamide on pyrolysis, is a similar case,

[9] Kirpal, *Monatsh.*, 1908, **29**, 227; Fibel and Spoerri, *J. Amer. Chem. Soc.*, 1948, **70**, 3908.
[10] Metzler and Snell, *ibid.*, 1955, **77**, 2431; Albert and Phillips, *J.*, 1956, 1294.

although here the serine unit is attached as an oxazoline ring.[11] Antimycin [12] also has an aromatic system attached to an α-amino-β-hydroxy-acid (threonine) and appears to give an amide on thermal treatment though this compound has not been identified. As the actinomycins are comparatively stable to thermal treatment it seems that for amide elimination to occur under fairly mild conditions a phenolic group or the equivalent in the *ortho*-position is probably a structural requirement.

In addition to alanine, leucine, and hydroxyproline reported earlier, we have identified threonine and sarcosine in the products of complete hydrolysis of the antibiotic. Prolonged treatment of viridogrisein with cold aqueous alkali gives some leucylhydroxyproline, identified (tentatively) by hydrolysis and paper chromatography and by the purple colour it gives with ninhydrin which excludes the possibility of an *N*-terminal hydroxyproline residue.[13] The structure of this dipeptide is in accord with the order of the amino-acid units shown in formula (I).

The remarkable similarity between the actinomycins and viridogrisein concerning the position of the threonine unit and the amino-acid sequence and lactonic nature of the peptide raises the question of the biogenesis. Observations by Brenner's school [14] that



amino-acids can be inserted into a peptide containing serine, threonine, or cysteine by esterification of the amino-acid to be inserted with the free hydroxyl or thiol groups invites the suggestion that cyclic peptides containing threonine, serine, etc., could be built up by ring expansion based on the insertion principle starting, in the case of viridogrisein, with the cyclic dipeptide (dioxopiperazine) of L-phenylsarcosine and L-threonine. Insertion of L-alanine would give the cyclic tripeptide, L-phenylsarcosyl-L-threonyl-L-alanyl and so on. The macrocyclic lactone could be obtained from a cyclic threonyl (or seryl) peptide by an *N*- ⟶ *O*-acyl rearrangement, thereby releasing an amino-group for the final condensation with 3-hydroxypicolinic acid. In the actinomycins the aromatic acid is 3-hydroxy-4-methylanthranilic acid and the phenoxazin-3-one nucleus is formed by a final oxidative coupling [15] of the *o*-aminophenol.

Experimental

Light-absorption figures are given for EtOH solutions except where otherwise stated.

Purification of Viridogrisein.—Crude viridogrisein (4 g. of 90%) was dissolved in saturated ethanolic ammonia (40 c.c.) with shaking. Next day the crystalline precipitate was separated, washed with ethanolic ammonia (10 c.c.), and heated *in vacuo* at 100° for 1 hr., to give viridogrisein (2·84 g.) as a colourless amorphous powder, m. p. 163—165° (decomp.) (Found: C, 59·0; H, 7·05; N, 12·3; NMe, 5·35. Calc. for $C_{44}H_{62}O_{11}N_8,H_2O$: C, 58·9; H, 7·2; N, 12·5; 3NMe, 5·0%), $\lambda_{max.}$ 304 mμ (log ε 3·93).

Di-O-acetylviridogrisein.—Viridogrisein (430 mg.) was dissolved in acetic anhydride (2 c.c.) containing 60% perchloric acid (1 drop). After 24 hr. at room temperature, the solution was poured into water and extracted with chloroform (3 × 50 c.c.). The combined extracts were washed with aqueous sodium hydrogen carbonate and then dried. After removal of the solution, the gummy residue was purified by repeated precipitation from ethyl acetate with light petroleum (b. p. 60—80°) to give the diacetate as a colourless granular solid (Found: C, 58·9; H, 6·95; N, 11·8; Ac, 8·8. $C_{48}H_{66}O_{13}N_8,H_2O$ requires C, 58·8; H, 6·8; N, 11·4; 2Ac, 8·8%), light absorption: $\lambda_{max.}$ in EtOH 270 mμ (log ε 3·55), in N/100-HCl 269 mμ (log ε 3·60), and in N/100-NaOH 338 mμ (log ε 3·82).

[11] Snow, *J.*, 1954, 2588, 4080.
[12] Tener, van Tamelen, and Strong, *J. Amer. Chem. Soc.*, 1953, **75**, 3623.
[13] Johnson and McCaldin, *J.*, 1958, 817.
[14] Brenner, Zimmermann, *et al.*, *Helv. Chim. Acta*, 1957, **40**, 1497, 1933.
[15] Brockmann and Muxfeldt, *Angew. Chem.*, 1956, **68**, 69; Hanger, Howell, Johnson, *et al.*, *J.*, 1957, 1592; 1958, 496.

XUM

Viridogriseic Acid.—Viridogrisein (3 g.) was dissolved in 2N-aqueous sodium hydroxide (18 c.c.), kept overnight at 0°, for a further 18 hr. at room temperature, and then neutralised with 2N-hydrochloric acid. The gummy precipitate was extracted with ethylene dichloride (2 × 50 c.c.) and chloroform (50 c.c.). The combined extracts were dried and concentrated to 7 c.c.; addition of ether (150 c.c.) then gave a gum which was reprecipitated from ethanol with ether. The gum so formed slowly solidified (2·25 g.) and was further purified by reprecipitation from ethyl acetate with light petroleum (b. p. 60—80°), being obtained as a colourless amorphous solid, m. p. 96—100° (decomp.) after drying at 20°, m. p. 138—140° (decomp.), after drying at 130° (Found: C, 58·3; H, 7·15; N, 12·1. Calc. for $C_{44}H_{64}O_{13}N_8,H_2O$: C, 58·4; H, 7·35; N, 12·4%), $\lambda_{max.}$ in $CHCl_3$ 307 mμ (log ε 3·92), in N/100-HCl 304 mμ (log ε 3·93), and in N/100-NaOH 333 mμ (log ε 3·93).

Pyrolysis of Viridogrisein.—(i) Viridogrisein (5·0 g.) was heated at 220°/0·1 mm. for 5 hr. and the gummy sublimate which was obtained on a cold finger was dissolved in chloroform (100 c.c.) and extracted with N-sodium hydroxide (3 × 100 c.c.). The combined aqueous extracts were adjusted to pH 6 with hydrochloric acid and extracted with chloroform (4 × 200 c.c.). The chloroform extracts were washed, dried, and evaporated to a pale brown residue (511 mg.) which was sublimed at 100°/0·1 mm.; this yielded colourless crystals (359 mg.) which recrystallised from chloroform as feathery needles, m. p. 193—194°, not depressed when mixed with authentic 3-hydroxypicolinamide (Found: C, 52·2; H, 4·5; N, 20·5. Calc. for $C_6H_6O_2N_2$: C, 52·2; H, 4·4; N, 20·3%), $\lambda_{max.}$ 224 and 302 mμ (log ε 3·83 and 3·84). The infrared spectrum (KBr) showed max. at 777, 807, 866, 1237, 1265, 1302, 1338, 1438, 1453, 1594, 1616, 1691, 3205, and 3406 $cm.^{-1}$.

The dark brown residue from the pyrolysis was treated with boiling 4N-hydrochloric acid for 4 hr., the distillate being collected in a solution of 2 : 4-dinitrophenylhydrazine (750 mg.) in 4N-hydrochloric acid (500 c.c.). The resulting cloudy, orange solution was extracted with chloroform (6 × 100 c.c.), and the combined chloroform extracts were washed with water (100 c.c.) and dried. After removal of the solvent, the residue was chromatographed in benzene on alumina (Spence type H) (40 × 3·5 cm.). The main band was eluted with benzene and after removal of the solvent, the 2 : 4-dinitrophenylhydrazone was obtained as orange plates (283 mg.) which after crystallisation from methanol had m. p. 124—125° alone or when mixed with the authentic derivative of acetone (Found: C, 45·4; H, 4·3; N, 23·6. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·2; N, 23·5%).

(ii) Viridogrisein (162 mg.) was heated in dry pyridine (2 c.c.) in a sealed tube at 160° for 14 hr. After removal of the solvent, the residue was sublimed at 120°/1 mm. to give 3-hydroxypicolinamide (9 mg.) which crystallised from chloroform as colourless needles, m. p. and mixed m. p. 193—194°.

Ethyl 3-Hydroxypicolinate.—3-Hydroxypicolinic acid [9] (508 mg.) was heated in ethanol (25 c.c.) containing sulphuric acid (1 c.c.) for 6 hr. The product was concentrated to 10 c.c., diluted with water (to 75 c.c.), adjusted to pH 6 with aqueous sodium hydroxide, and extracted with chloroform (3 × 50 c.c.). The chloroform extracts were washed with water (2 × 50 c.c.), then dried and the solvent was removed. The residual oil was distilled to give the *ester* as a colourless liquid (300 mg.) (Found: C, 57·2; H, 5·1; N, 8·4. $C_8H_9O_3N$ requires C, 57·5; H, 5·4; N, 8·4%), $\lambda_{max.}$ 226 and 302 mμ (log ε 3·96 and 4·05).

3-Hydroxypicolinamide.—The foregoing ester (101 mg.) was added to saturated ethanolic ammonia (2·5 c.c.), a white precipitate of the ammonium salt of the ester being formed immediately. A sample of the precipitate was removed but decomposed rapidly, leaving an oily residue. The precipitate dissolved when the reaction mixture was heated in a sealed tube; heating was continued at 110° for 16 hr., after which the solvent was removed and the colourless solid residue sublimed at 100°/0·1 mm. to give the *product* (67 mg.) which crystallised from chloroform as feathery needles, m. p. 192—194° (Found: C, 52·1; H, 4·55; N, 20·1%), $\lambda_{max.}$ 224 and 302 mμ (log ε 3·81 and 3·84).

Ammonolysis of Viridogrisein.—Viridogrisein (5·43 g.) was dissolved in ethanol (10 c.c.), and aqueous ammonia (*d* 0·88; 100 c.c.) was added. The clear solution was kept in a stoppered flask at room temperature for 51 hr., then boiled briefly to expel ammonia, adjusted to pH 6 with hydrochloric acid, and extracted with chloroform (3 × 75 c.c.). The combined chloroform extracts were shaken with saturated aqueous sodium hydrogen carbonate (2 × 150 c.c.). The aqueous layers were combined, adjusted to pH 6 with hydrochloric acid, and extracted with chloroform (3 × 75 c.c.). These chloroform extracts were washed with water (100 c.c.), dried

(Na_2SO_4), and evaporated, giving viridogriseic acid monohydrate, as a white amorphous powder (1·49 g.), m. p. 96—100° (decomp.) after drying *in vacuo* at 20°, m. p. 137—140° (decomp.), after drying *in vacuo* at 130°.

The original chloroform extracts, when washed with water (2 × 75 c.c.), dried (Na_2SO_4), and evaporated, gave a pale yellow amorphous powder (viridogriseamide) (3·09 g.). The product was purified through the crystalline ammonium salt by the method used for viridogrisein, giving the *amide* as a white amorphous powder, m. p. 165—170° (decomp.) (Found, in a sample dried at 140° *in vacuo*: C, 59·1; H, 7·15; N, 14·1. $C_{44}H_{65}O_{11}N_9$ requires C, 58·9; H, 7·3; N, 14·1%), $\lambda_{max.}$ 304 mμ (log ε 3·92).

Hofmann Degradation of Viridogriseamide.—Bromine (2·4 g.) was added dropwise with stirring to a solution of sodium hydroxide (3·8 g.) in water (45 c.c.) at 2°. After the bromine had dissolved, viridogriseamide (2·43 g.) was added gradually with stirring. The solution was stirred at 0—2° for 1½ hr., then sodium hydroxide (3·0 g.) was added, and the solution heated on the water-bath for 2 hr. The solution then gave a positive Nessler's test. After being washed with chloroform (2 × 50 c.c.) the solution was acidified with concentrated hydrochloric acid (35 c.c.) and extracted with ether (4 × 50 c.c.). The combined ether extracts were washed with water (50 c.c.) and dried (Na_2SO_4), and the solvent was removed. The brown semi-crystalline residue was sublimed at 60°/0·1 mm., giving benzoic acid (11 mg.), m. p. and mixed m. p. 121°.

Paper-chromatographic Examination of the Acid Hydrolysate of Viridogrisein.—Viridogrisein (20 mg.) was heated in 6N-hydrochloric acid (1 c.c.) in a sealed tube at 120° for 18 hr. After removal of the hydrochloric acid the residue was redissolved in water (2 c.c.), and the solution used for two-dimensional paper chromatography by the ascending technique. The developing solvents were butan-1-ol–acetic acid–water (4 : 1 : 5) and phenol–water. After drying, the papers were sprayed with ninhydrin solution and then heated at 110° for 10 min. Seven coloured spots were observed (R_F values for the butanol solvent given first; colours purple except where otherwise stated): (i) 0·20, 0·70 (yellow, hydroxyproline); (ii) 0·23, 0·75 (pink, sarcosine); (iii) 0·26, 0·47 (threonine); (iv) 0·31, 0·55 (alanine); (v) 0·53, 0·87 (colourless but fluorescent in ultraviolet light before ninhydrin treatment, 3-hydroxypicolinic acid); (vi) 0·58, 0·95; (vii) 0·62, 0·82 (leucine); (viii) 0·72, 0·97. Spots (vi) and (viii) are now known [4] to correspond to *N*-phenylsarcosine and β-*N*-dimethyl-leucine. The R_F values were checked against the appropriate amino-acid standard.

Deamination of Viridogrisein Hydrolysate.—Viridogrisein was hydrolysed as described in the previous experiment, and the solution diluted with water (10 c.c.) and treated with nitrous fumes for 1 hr. The solution was heated under reflux for 30 min. and then after removal of the solvent the residue was redissolved in water (2 c.c.) and used for paper-chromatographic examination (ascending technique) in the butan-1-ol–acetic acid–water solvent. After development with ninhydrin four spots (R_F values given) were observed: (i) 0·12 (yellow, hydroxyproline); (ii) 0·18 (sarcosine); (iii) 0·53; (iv) 0·65. Using methanol–pyridine–water (20 : 5 : 1) also gave four spots: (i) 0·43 (yellow, hydroxyproline); (ii) 0·49 (sarcosine); (iii) 0·68 (brown); and (iv) 0·76.

Partial Hydrolysis of Viridogrisein.—Viridogrisein (2·07 g.) was dissolved in 0·3N-aqueous barium hydroxide (100 c.c.) and kept at room temperature for 8 weeks. Then it was neutralised (pH 7) with sulphuric acid, filtered from barium sulphate, washed with chloroform (3 × 100 c.c.) (to remove viridogriseic acid), and taken to dryness, giving a pale brown amorphous residue (1·60 g.). This was subjected to partition chromatography on powdered cellulose (30 × 4 cm.) in the system butan-1-ol–acetic acid–water (4 : 1 : 5), and fractions (10 c.c.) were collected. Alternate fractions were examined by paper chromatography in the same solvent system: those up to no. 39 contained no ninhydrin-positive substances; fractions 41—61 contained leucine (R_F 0·55); fractions 67—93 contained a substance (purple spot; R_F 0·45) which did not correspond with any of the amino-acids in viridogrisein. These fractions were taken to dryness, giving a pale brown solid residue (40 mg.) which did not crystallise. Hydrolysis with 6N-hydrochloric acid at 120° for 12 hr. gave hydroxyproline (yellow spot; R_F 0·16) and leucine (R_F 0·55) when examined by paper chromatography in the same solvent system.

We thank Messrs. Parke Davis and Co. Ltd., for their generous gift of viridogrisein as well as a Maintenance Grant (to A. B. M.). The award of a Maintenance Grant (to R. B. A.) from the Department of Scientific and Industrial Research is also gratefully acknowledged.

THE UNIVERSITY, NOTTINGHAM. [*Received, July 9th,* 1958.]

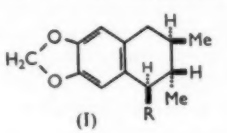
902. *Some Stereochemical Studies of Lignans.*

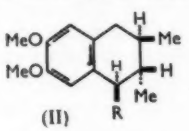
By A. J. Birch, Barton Milligan, (Mrs.) E. Smith, and R. N. Speake.

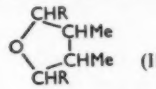
(−)-Galcatin (I) * has been converted into (−)-galbulin (II). The steric configurations of (−)-galbelgin and galgravin (isomeric forms III) have been investigated by fission of the tetrahydrofuran ring with sodium and ethanol in liquid ammonia, and examination of the products. Reduction of (±)-1 : 2-(VII) and (±)-3 : 4-dehydrogalbulin (VIII) by lithium and ammonia leads predominantly to (±)-galbulin which accordingly has the configuration (II + its enantiomer). The action of perchloric acid in acetic acid on galgravin and galbelgin has been investigated. We conclude that galgravin is probably (XII) and galbelgin probably (XIV).

The lignans (−)-galbulin (II), (−)-galbacin (III; but with R = 3 : 4-methylenedioxyphenyl), (−)-galcatin (I), galgravin, and (−)-galbelgin, the last two being stereoisomeric forms of (III), were isolated from *Himantandra* barks.[1] They offer opportunities for stereochemical studies since they carry only methyl groups instead of the oxygenated side-chains hitherto usually encountered in this series. While the present work was in progress, Schrecker and Hartwell [2] also carried out investigations in this field and arrived at some similar conclusions although by different routes.

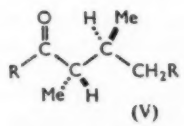
(−)-Galcatin (I) has the same optical configuration as (−)-galbulin (II) since it can be converted into the latter by alkaline demethylenation and methylation. Schrecker and Hartwell [2] concluded on the basis of optical rotations that this relation was highly probable.

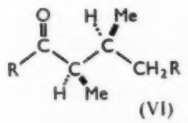

(I)

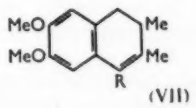

(II)

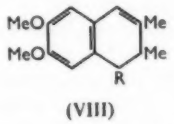

(III)

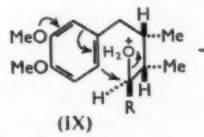
R·CH(OH)·CHMe·CHMe·CH$_2$R (IV)

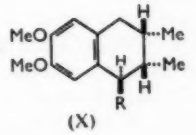

(V)


(VI)


(VII)


(VIII)


(IX)


(X)

R = 3:4-(MeO)$_2$C$_6$H$_3$

Galbelgin.—The lignan mixture from *Himantandra belgraveana* F.v.Mull. has now been found to contain the optically active lignan (III) already obtained [1] from (−)-galbacin (III; but R = 3 : 4-methylenedioxyphenyl). We have accordingly named it galbelgin. The lignan mixtures appear to differ somewhat in composition from specimen to specimen of bark; in some samples no galbelgin could be detected.

Steric Configurations of Galbelgin, Galgravin, and Galbulin.—Galgravin and galbelgin are stereoisomers (III). The former is optically inactive and so are its derivatives, and it is accordingly probably the *meso*-form since in only one case [3] has an inactive lignan been encountered where optical activity is possible. The methyl groups are therefore

* This and other formulæ represent absolute configurations, except that for (±)-forms only one form is shown.

[1] Hughes and Ritchie, *Austral. J. Chem.*, 1954, **7**, 104.
[2] Schrecker and Hartwell, *J. Amer. Chem. Soc.*, 1955, **77**, 432.
[3] Carnmalm and Erdtman, *Chem. and Ind.*, 1955, 570.

probably *cis*. In order to investigate the stereochemistry of the carbon skeleton, galgravin and galbelgin were reduced with sodium in liquid ammonia to stereoisomers (IV) which on cyclisation with perchloric acid in acetic acid gave respectively (±)-*iso*galbulin (X), m. p. 88°, and (−)-galbulin (II), m. p. 132°. Previously [4] the cyclisation of dihydrogalgravin (IV) was erroneously stated to produce an isomer of galbulin, m. p. 117°; this apparently arose from a confusion of specimens. The (±)-*iso*galbulin is structurally identical with the (+)-*iso*galbulin obtained by Schrecker and Hartwell [2] from β-conidendryl alcohol dimethyl ether. We are indebted to Dr. Hartwell for a comparison of infrared spectra: the result shows that the methyl groups are *cis*-orientated in galgravin and *trans*-orientated in galbelgin.[2] Before this was known, we had obtained indications in the same sense from other directions.

In these cyclisations the configuration of the asymmetric centre next to the hydroxyl group is unchanged. This indicates that cyclisation proceeds directly through the cation (*e.g.*, IX) rather than through an anhydro-compound.

Dihydrogalgravin (IV) on oxidation with chromic anhydride in pyridine gave the ketone dehydrodihydrogalgravin (V). In this substance there remain only the asymmetric centres associated with the methyl groups, and one of these is adjacent to the carbonyl group. Treatment with sodium ethoxide in ethanol or chromatography on alkaline alumina left the ketone unchanged. This is a strong indication that it has the sterically less compressed conformation (V) derived from the tetrahydrofuran ring (III) with *cis*-methyl groups rather than the more compressed (VI) derived from the *trans*-methyl compound. That inversion had not occurred during oxidation was shown by reduction of the ketone with lithium aluminium hydride in high yield back to dihydrogalgravin.

The isolation of (−)-dihydroguaiaretic acid dimethyl ether as a minor product in the reduction of galbelgin with sodium and liquid ammonia confirms the *trans*-orientation of the methyl groups in galbelgin. Reduction of galgravin under somewhat more drastic conditions than those previously described [4] gave a poor yield of *meso*-dihydroguaiaretic acid dimethyl ether, which is further confirmation of the *cis*-methyl groups in galgravin.

Cyclisation of the ketone (V) with polyphosphoric acid gave a (±)-1 : 2-dehydrogalbulin (VII) isomeric with the 3 : 4-dehydrogalbulin (VIII) obtained by direct cyclisation of galgravin.[1]

Dihydrogalbelgin on oxidation with chromic anhydride in pyridine apparently gave the desired ketone as shown by the spectra of the product; the ultraviolet absorption curve in particular was almost identical with that of dehydrodihydrogalgravin, the ε values being about 5% lower. The substance could not be crystallised, however, and lack of material prevented further investigation.

The most difficult configurations to determine in this series are those of the asymmetric centres carrying the 3 : 4-dimethoxyphenyl groups in galgravin and galbelgin; in fact, to no tetrahydrofuranoid lignan has a complete assignment been made. The problem could be approached by oxidation of the benzene rings, but we have attempted to attack it from other directions.

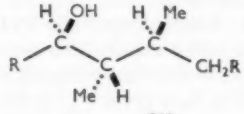
The reduction by lithium aluminium hydride of dehydrodihydrogalgravin (V) to dihydrogalgravin (IV = XI) would give information about the orientation of one R·CH·O· group in galgravin if its steric course were known, and of both if galgravin has the *meso*-configuration. The AlH_4^- ion should attack the least hindered side of the carbonyl group of the ketone (V),[5] producing the alcohol (XI). On this basis, and on the assumption that galgravin is a *meso*-compound (an assumption supported to some extent by the isolation of only one dihydrogalgravin from the original reduction), galgravin should be the *trans-meso*-isomer (XII). Dihydrogalgravin is oxidised 1·4—1·6 times as fast as dihydrogalbelgin by chromic anhydride in pyridine to the corresponding ketone. The oxidation

[4] Birch, Hughes, and Smith, *Austral. J. Chem.*, 1954, **7**, 83.
[5] Cram and Abdel Hafez, *J. Amer. Chem. Soc.*, 1952, **74**, 5828.

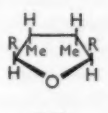
XUM

was followed in both cases by absorption at 302 mμ where the ketones absorb strongly and the alcohols weakly. Although the ketone from dihydrogalbelgin has failed to crystallise its absorption is nearly identical with that from dihydrogalgravin. This result appears to indicate that the hydrogen atom in the *H*·C·OH group of dihydrogalbelgin is more hindered sterically than the similar one in dihydrogalgravin. This conclusion follows from Westheimer's work [6] which indicates that the dominant factor in such oxidations is the degree of hindrance experienced by the hydrogen atom rather than that experienced by the hydroxyl group. The structure indicated for dihydrogalbelgin is therefore (XIII), and if it is assumed that the isolation of only one substance from the original reduction of galbelgin indicates identical steric environment for the 3 : 4-dimethoxyphenyl rings, then galbelgin has formula (XIV). If the last assumption is incorrect one other formula is possible, that with *cis*-related aromatic rings.

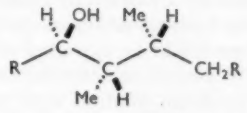
It is clear from models that forms (XI) and (XIII) are the thermodynamically stable ones for compounds containing *cis*- and *trans*-methyl groups respectively. This can be investigated by examining the acid-catalysed reactions of galgravin and galbelgin; we have found that the best reagent for the purpose is a dilute solution of perchloric acid in acetic acid. Reaction proceeds initially through an oxonium salt, leading to an equili-



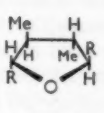
(XI)



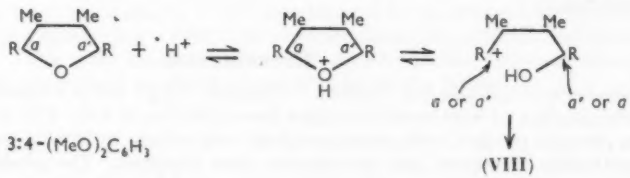
(XII)



(XIII)



(XIV)



R = 3:4-$(MeO)_2C_6H_3$

(VIII)

brium of the type shown, with equilibration of the centres at *a* and *a'*, and in the present series to final irreversible cyclisation and dehydration to the naphthalene derivative (VIII).

Such reactions might be used in two ways to study the relative steric compressions in molecules of the same series. One method is to study the positions of equilibria between stereoisomers; the other is to study rates of cyclisation to compound (VIII).

The position of an equilibrium seems from models to depend chiefly on the steric compressions due to the aromatic rings in their interferences with the adjacent methyl groups or to interference of the methyl groups with each other. With both galgravin and (−)-galbelgin treatment to incipient cyclisation, as shown by increasing absorption at 280 mμ, resulted in substantial recovery of the starting material as the only crystalline product. A stereoisomer of galgravin synthesised by Haworth and Blears has been converted by a similar process of equilibration into galgravin itself,[7] which is further evidence that the latter is the stable isomer. These results again lend support to the formulations (XII) and (XIV) for galgravin and galbelgin respectively.

Rates of cyclisation to the aryldihydronaphthalene (*e.g.*, VIII) would be expected to depend on the concentration of carbonium ion, and the rate-determining stage will therefore be the fission of the oxonium ring. This in turn will be related to the steric compression in the substance equilibrated at centres *a* and *a'* if equilibration is rapid compared with cyclisation. This expectation was confirmed by the fact that the rates of cyclisation of galgravin and of Haworth and Blears's less stable isomer were found to be identical.

[6] Westheimer, *Chem. Rev.*, 1949, **45**, 419; Barton, *Experientia*, 1950, **6**, 317.
[7] Professor R. D. Haworth, personal communication.

Galbelgin cyclised at least six times more slowly than galgravin under identical conditions, cyclisation being measured by increased absorption at 280 mμ. This further supports the assumption of *trans*-methyl groups in the former and *cis*-methyl groups in the latter.

(−)-Galbacin (XIV; but R = 3 : 4-methylenedioxyphenyl) was cyclised much more slowly than galbelgin of identical configuration. This is probably due to slower fission of the oxonium salt because of smaller ability of the 3 : 4-methylenedioxyphenyl ring to stabilise the carbonium ion.

Further evidence bearing on the configuration of the 1-(3 : 4-dimethoxyphenyl) ring in galbulin (II) has been discussed by Schrecker and Hartwell.[2] It is probably *trans* to the adjacent methyl group, since the less compressed isomer would be expected from cyclisation of the intermediate cation of the type (IX).[8] This is supported by the synthesis [9] of what is almost certainly (±)-galbulin, by a series of reactions which would be expected to give the thermodynamically stable isomer at each stage. Further evidence is now provided by reduction with lithium in liquid ammonia of the isomeric dehydrogalbulins (VII) and (VIII); crystalline (±)-galbulin was isolated in over 50% yield in each case as the only crystalline product. It must be the thermodynamically stable *trans-trans*-isomer (II) since it is clear from models that there is no likelihood of formation of a less stable isomer by a kinetically controlled reaction (cf. ref. 10).

Finally, catalytic hydrogenation of *cyclo*galgravin [(±)-3 : 4-dehydrogalbulin (VIII)] under mild conditions might be expected to cause the methyl group attached to the new asymmetric centre to assume the *cis*-relation to the bulky 1-(3 : 4-dimethoxyphenyl) ring. Hydrogenation in alcoholic solution with palladium–charcoal in fact gives (±)-galbulin, m. p. 116—117°. All the evidence therefore points to the *trans-trans*-structure (II) for this substance.

Experimental

Conversion of Galcatin into Galbulin.—Galcatin (1·8 g.) and a solution from sodium (1·5 g.) in methanol (30 c.c.) were heated in a glass-lined autoclave at 150—170° for 12 hr. Methylation of the phenolic product with methyl sulphate and sodium hydroxide gave a gum with which the methoxide treatment and methylation were repeated. The product (1 g.) crystallised from methanol and had m. p. 130—132° undepressed by authentic (−)-galbulin (m. p. 132°).

Isolation of Galbelgin.—The mother-liquors from the crystallisation of galgravin [1] gave on slow evaporation two obviously different kinds of crystal. These were separated by hand-picking: one lot was galgravin, m. p. 121°; the other was identical with the product obtained [1] by demethylenation and methylation of (−)-galbacin and had m. p. 138°, $[\alpha]_D$ −102° (*c* 0·04 in chloroform). In this case the ratio of total galgravin to galbelgin was about 30 : 1.

Dihydrogalgravin and Dihydrogalbelgin.—The reduction with sodium and ethanol in liquid ammonia of galgravin has been described.[4] Galbelgin (600 mg.) in ethylene glycol dimethyl ether (20 c.c.) and liquid ammonia (25 c.c.) was reduced by addition of sodium (125 mg.). After 7 min. a blue colour still persisted and was discharged by the addition of a few drops of ethanol followed by water (2 c.c.). The ammonia was removed and the product extracted with ether. It partially crystallised and the solid was recrystallised from methanol to give (−)-dihydroguaiaretic acid dimethyl ether, $[\alpha]_D^{24}$ −24° (*c* 0·26 in chloroform), m. p. 88° undepressed by an authentic specimen. The infrared spectra were also identical. The recorded values [2] are m. p. 86—87°, $[\alpha]_D$ −31° (*c* 1·52 in chloroform). The yield was only a few mg. The main bulk of *dihydrogalbelgin* crystallised from the methanol mother-liquors after dilution with water and, recrystallised from aqueous ethanol (300 mg.), had m. p. 104°, $[\alpha]_D$ −94° (*c* 1·0 in chloroform) (Found: C, 70·2; H, 8·0. $C_{22}H_{30}O_5$ requires C, 70·6; H, 8·0%). This substance (100 mg.) in ethanol (5 c.c.) and concentrated hydrochloric acid (1 c.c.) was left for 3 days. Dilution with water and crystallisation from ethanol gave (−)-galbulin, m. p. 130—131° (Found: C, 73·6; H, 8·1. Calc. for $C_{22}H_{28}O_4$: C, 74·1; H, 7·9%).

Dihydrogalgravin similarly treated gave (±)-*iso*galbulin, $[\alpha]_D$ 0°, m. p. 88° (Found: C, 73·8;

[8] Haworth and Slinger, *J.*, 1940, 1321; 1942, 448.
[9] Muller and Vajda, *J. Org. Chem.*, 1952, **17**, 800.
[10] Birch, Smith, and Thornton, *J.*, 1957, 1339; Birch, Smith, and Wilson, unpublished work.

XUM

H, 7·8. Calc. for $C_{22}H_{28}O_4$: C, 74·1; H, 7·9%). The infrared spectrum of its chloroform solution is identical with that of (+)-*iso*galbulin.

Conversion of Galgravin into meso-*Dihydroguaiaretic Acid Dimethyl Ether.*—Galgravin 750 mg.) in "dimethyloxitol" (ethylene glycol dimethyl ether) (10 c.c.) and liquid ammonia (50 c.c.) was reduced by adding sodium (about 6 equivs.) until the blue colour persisted for 10 min. Ethanol (1 c.c.) was added, followed by water. The product was worked up in the usual way and the fraction least soluble in aqueous ethanol proved to be *meso*-dihydroguaiaretic acid dimethyl ether (60 mg.), m. p. 101°, undepressed by an authentic specimen (m. p. 102°) which had an identical infrared spectrum. The mother-liquor yielded some dihydrogalgravin, but a gum was also present.

Dehydrodihydrogalgravin.—Dihydrogalgravin (400 mg.) in pyridine (5 c.c.) was added to chromic anhydride (400 mg.) and pyridine (3 c.c.). Next morning the mixture was added to water and extracted with ether which was washed with dilute hydrochloric acid. The resulting *dehydrodihydrogalgravin* (340 mg.), crystallised from ethanol, had m. p. 105°, $\lambda_{max.}$ 229, 275, 302 mμ (log ε 4·42, 4·13, 3·92), $\lambda_{min.}$ 247, 294 mμ (log ε 3·45, 3·92), $\nu_{max.}$ 1675 cm.$^{-1}$ (Found: C, 70·6; H, 7·6. $C_{22}H_{26}O_5$ requires C, 71·0; H, 7·5%). This material depressed the m. p. of the starting material and its infrared spectrum contained no hydroxyl band. Attempts to isomerise it with 5% ethanolic sodium ethoxide at 20° during 3 weeks, or on the steam-bath for 2 hr., gave only a substantial recovery of ketone, m. p. and mixed m. p. 102—105°.

Similar oxidation of dihydrogalbelgin gave only a gum, but the infrared band at 1675 cm.$^{-1}$, the lack of a hydroxyl band, and identity of the ultraviolet spectrum with that above (ε 95% of those given) showed that oxidation had resulted.

Comparative oxidations of dihydrogalgravin and dihydrogalbelgin were carried out side by side with the same reagents. Finely powdered chromic anhydride (150 mg.) was added to "AnalaR" pyridine (5 c.c.). After 3 minutes' shaking, portions (1·00 c.c.) were added to samples (10 mg.) of the two alcohols. After an arbitrary time (0·5—5 hr.) the partially oxidised products were extracted and the quantity of ketone estimated by its ultraviolet absorption at 302 mμ (dehydrodihydrogalgravin log ε 3·92). In all experiments the galbelgin derivative was oxidised more slowly. The rates appeared to depend greatly on the particular sample of reagent. The following are typical results of two runs at successive times:

	Run I			Run II		
Dehydrodihydrogalbelgin	7	35	81%	38	44	63%
Dehydrodihydrogalgravin	10	50	100%	48	65	98%

(±)-1 : 2-*Dehydrogalbulin.*—Dehydrodihydrogalgravin (150 mg.) was rapidly stirred into a mixture of phosphoric acid (1 c.c.) and phosphoric oxide (1 g.) at 70° and the temperature raised during 1 min. to 90°; then water (5 c.c.) was added. Extraction with ether and crystallisation from ethanol gave (±)-1 : 2-*dehydrogalbulin*, m. p. 116° (Found: C, 74·5; H, 7·5. $C_{22}H_{26}O_4$ requires C, 74·6; H, 7·4%). Some unchanged starting material was recovered. With longer heating considerable dehydrogenation occurred to the phenylnaphthalene derivative,[1] m. p. 178°.

Reduction of Dehydrodihydrogalgravin.—Dehydrodihydrogalgravin (50 mg.) and lithium aluminium hydride (50 mg.) in pure ether (20 c.c.) were left at room temperature with occasional shaking for 30 min. A little ethyl acetate was added, the mixture poured into water, and the product extracted with ether. After crystallisation from aqueous methanol, the product (40 mg.), m. p. 108°, was identified as dihydrogalgravin by mixed m. p. and infrared spectra.

Attempted Isomerisations of Galgravin and Galbelgin.—The lignan was treated with 1·2% solution of perchloric acid in acetic acid at room temperature until the presence of cyclised material was shown by increased light absorption at 280 mμ. Working up afforded only a substantial amount of starting material.

*Cyclisations of Galgravin, Galbelgin, and the all-*cis(?)-*Isomer.*—The lignans were treated as above (0·1% solution in acetic acid) and the extent of cyclisation calculated from the absorptions at 280 mμ: galgravin, galbelgin log ε 3·82; *cyclo*-derivatives $\lambda_{max.}$ 280 mμ (log ε 4·17) [also found is a peak at $\lambda_{max.}$ 225 mμ (log ε 4·55)]. *cyclo*Galbelgin [(−)-3 : 4-dihydrogalbulin] had m. p. 97—98°, $[\alpha]_D$ +125° (*c* 0·85 in chloroform) (Found: C, 74·7; H, 7·3. Calc. for $C_{22}H_{26}O_4$: C, 74·6; H, 7·4%). The relative rates of cyclisation, measured at small conversions, and on the basis of unimolecular kinetics are: galgravin 1·0; galbelgin 0·17; all-*cis*(?)-isomer (m. p. 133°) 1·0. Under identical conditions galbacin cyclised at a relative rate <0·02 ($\lambda_{max.}$ 287 mμ).

Reduction of (±)-**1 : 2-** *and* (±)-**3 : 4-***Dehydrogalbulin.*—Lithium (10 mg.) was added to (±)-**1 : 2**-dehydrogalbulin (95 mg.) in dry ether (2 c.c.) and liquid ammonia (20 c.c.). The solution became first scarlet, and then deep blue. After 5 min. solid ammonium chloride was cautiously added, followed by water (5 c.c.). Ether-extraction, followed by crystallisation of the product from aqueous ethanol, gave (±) galbulin (50 mg., 53%), m. p. 117°, identified by mixed m. p. and infrared spectrum.

(±)-**3 : 4**-Dehydrogalbulin (*cyclo*galgravin), m. p. 88—89° (100 mg.), similarly reduced gave (±)-galbulin (55 mg.), m. p. 117°.

Hydrogenation of (±)-**3 : 4**-dehydrogalbulin (100 mg.) with palladium–charcoal in ethanol gave (±)-galbulin (70 mg.), m. p. 116—117°.

We are indebted to the late Dr. G. K. Hughes and Dr. E. Ritchie for generous gifts of extracts from *Himantandra* barks, to Mr. L. J. Webb and Mr. J. G. Tracey (C.S.I.R.O.) for collection of botanical material, to the Department of Scientific and Industrial Research for a Scholarship (to R. N. S.), and to Dr. J. L. Hartwell for specimens of (−)- and *meso*-dihydroguaiaretic acid dimethyl ether.

Department of Organic Chemistry, University of Sydney.
The University, Manchester 13. [*Received, January 28th*, 1958.]

---

903. *The Biosynthesis of Polysaccharides. Part I. The Composition of Plum-leaf Polysaccharides.*

By P. Andrews and L. Hough.

Hydrolysis of the polysaccharides from Victoria plum leaf afforded mainly D-galactose, D-glucose, L-arabinose, D-xylose, and D-galacturonic acid. Smaller amounts of D-mannose, L-rhamnose, L-fucose, 2-*O*-methyl-D-xylose, 2-*O*-methyl-L-fucose, and glucuronic acid were also isolated. Some fractionation of the leaf polysaccharides was achieved by successive extractions with water and aqueous alkalis. The cellulose content has been investigated.

Preliminary results [1] on the incorporation of radioactive carbon into the components of plum-leaf polysaccharides as a result of photosynthesis in $^{14}CO_2$, suggested that after 48 hours the isotope was present in all the major monosaccharide constituents. In order to further these biosynthetic studies [2] it was necessary to characterise firmly the monosaccharide components and to investigate the fractionation of the polysaccharides.

Mature Victoria plum leaves were exhaustively extracted with methanol, and the insoluble residue, containing the polysaccharides, was heated with N-sulphuric acid for several short periods. From the combined hydrolysates were isolated three fractions, a mixture of neutral monosaccharides, small amounts of acidic oligosaccharides, and a degraded pectic acid fraction. The last was recognised by hydrolysis with a pectinase preparation [3] and with acid to give D-galacturonic acid which was characterised *via* the derived methyl ester methyl glycoside by reduction with borohydride to D-galactose.

Examination of a hydrolysate of the acidic oligosaccharide mixture by paper chromatography indicated the presence of traces of acidic oligosaccharides, together with glucurono-6 ⟶ 3-lactone, mono-*O*-methylhexuronic acid, glucuronic acid, and galacturonic acid. The last two hexuronic acids were recognised by reduction as above to glucose and galactose and isolation of D-galactose.

Fractionation of the neutral monosaccharides by formation of di-*O*-*iso*propylidene derivatives and subsequent selective hydrolysis [4] was not entirely satisfactory in view of the losses incurred, although D-glucose and D-xylose, and D-galactose and L-arabinose, were considerably enriched in separate fractions. Liberation of the free monosaccharides from

[1] Hough and Pridham, *Nature*, 1956, **177**, 1039.
[2] Andrews and Hough, *Biochem. J.*, 1957, **67**, 11P.
[3] Reid, *J. Sci. Food Agric.*, 1950, **1**, 234.
[4] Bell, *J.*, 1947, 1461.

the mixed *O-iso*propylidene derivatives by acid hydrolysis, followed by paper-chromatographic separations, eventually afforded crystalline specimens of D-galactose, D-glucose, L-arabinose, D-xylose, and L-rhamnose. D-Mannose was isolated as a syrup and characterised by conversion into its phenylhydrazone. Further hydrolysates of the leaf polysaccharides yielded sufficient L-fucose for subsequent characterisation.

Traces of unidentified reducing sugars which moved ahead of rhamnose on the paper chromatogram were also detected in the neutral sugar mixture. Adsorption of the mixture on a squat charcoal column [5] followed by fractional elution with ethanol–water afforded 2-*O*-methyl-D-xylose [6] and 2-*O*-methyl-L-fucose.[7] These *O*-methyl sugars have also been isolated from the alkali-stable component (" araban ") of sugar-beet pectin.[8] Springer, Ansell, and Ruelius [9] have obtained evidence, by paper chromatography and serological tests, for the presence of 2-*O*-methylfucose in the polysaccharides of yew twigs (*Taxus cuspidata*), and 2-*O*-methyl-xylose and -arabinose are reported to occur in Delaware soils.[10] These monosaccharides are unique in that they afford the only known instances of *O*-methylaldopentoses and of 2-*O*-methyl substitution amongst naturally occurring carbohydrates. Preliminary examination has now indicated that these *O*-methyl sugars are minor constituents of the polysaccharides of various leaves (*e.g.*, bean and clover) and of citrus pectins.

The relatively large number of monosaccharide constituents found in the leaf polysaccharides indicated that the latter formed a mixture of some complexity. This was corroborated by exhaustive extraction of the alcohol-insoluble leaf residue with cold water, hot water, cold N-sodium hydroxide, and hot 2·5N-sodium hydroxide in succession, and the subsequent isolation of a number of polysaccharide fractions (see Table). In general, each extract contained similar monosaccharide constituents, but in different relative proportions. The water-soluble polysaccharides resembled pectin, with galactose, arabinose, and galacturonic acid as the major constituents. Rhamnose formed a higher proportion (10—15%) of the cold-water fraction than of any other fractions; on the other hand glucose, a constituent of all the other fractions, was absent. In comparison, the fraction soluble in hot water was richer in arabinose, and the presence of xylose was noted. The polysaccharides extracted with alkali contained markedly increased proportions of glucose and xylose, and arabinose was still a major constituent, but galactose now formed only a small part of the total. The alkali-insoluble residue still contained the pentoses as well as glucose. The material remaining after treatment with acid chlorite contained starch and cellulose, the latter representing only a very small proportion (<1%) of the original leaf residue. An estimate of the cellulose content of the leaf residue, by Crampton and Maynard's method,[11] gave a value of 8·5%, but further examination of the cellulosic material obtained by this method indicated that the true value was of the order of 5%.

The wide variety of monosaccharides which occurs in the leaf accounts for all the monosaccharides found in other organs of the plant, including the fruit.[12] This suggests that the monosaccharides have their origin within the leaf structure and are initially incorporated into the attendant polysaccharides,[1,2] but that translocation to other parts of the plant might follow in due course.

Experimental

Partition chromatography, by the descending method, was carried out on either Whatman No. 1 or No. 540 filter paper, with one of the following solvent systems: (*a*) ethyl acetate–acetic acid–water (9 : 2 : 2 v/v); (*b*) butan-1-ol–pyridine–water (10 : 3 : 3 v/v); (*c*) butan-1-ol–ethanol–water (40 : 11 : 19 v/v). Sugars were detected on the chromatograms with *p*-anisidine

[5] Andrews, Hough, and Powell, *Chem. and Ind.*, 1956, 658.
[6] Andrews and Hough, *ibid.*, 1956, 1278.
[7] Anderson, Andrews, and Hough, *ibid.*, 1957, 1453.
[8] Andrews, Hough, Powell, and Woods, unpublished results.
[9] Springer, Ansell, and Ruelius, *Naturwiss.*, 1956, **11**, 256.
[10] Lynch, Olney, and Wright, *J. Sci. Food Agric.*, 1958, **9**, 56.
[11] Crampton and Maynard, *J. Nutrition*, 1938, **15**, 383.
[12] Pridham, Ph.D. Thesis, Bristol, 1955.

hydrochloride,[13] and the figures given for the relative amounts of monosaccharides in hydrolysates were obtained by visual comparison of their spot sizes; R_{Rh} is the rate of movement of a sugar on the chromatogram relative to rhamnose. Unless otherwise stated, hydrolyses were carried out in N-sulphuric acid at 100°, and evaporations were at 40° under reduced pressure. Amberlite ion-exchange resins were used throughout, and optical rotations were determined in water at 20°.

Plum leaves (*Prunus domestica* var. Victoria) were picked during August, and immediately immersed in alcohol. After removal of the stems, the leaves were continuously extracted with methanol in a Soxhlet apparatus. The alcohol-insoluble material was air-dried at 60°, and coarsely powdered (yield, about 15% w/w of fresh leaves) (Found: Moisture, 9·7%). Evaporation of the alcoholic extracts gave a dark solid (yield, about 8% w/w).

Hydrolysis of Alcohol-insoluble Leaf Residue.—A small portion of this material was hydrolysed for 16 hr. and after neutralisation with barium carbonate the hydrolysate was found by paper chromatography to contain galactose, glucose, arabinose, xylose, and hexuronic acid (*ca.* 1 : 2 : 2 : 1 : 1), with a smaller amount of rhamnose and traces of a compound with R_{Rh} 1·25 in solvent (*b*), which gave a pink colour with *p*-anisidine hydrochloride.

For isolation of the monosaccharides, alcohol-insoluble leaf residue (37 g.) was hydrolysed with acid (300 c.c.) for 4 hr., then the insoluble material was isolated on the centrifuge and again heated with acid (2 × 250 c.c.; 3 hr. each time). The final residue (R) was washed with hot water until the washings contained no carbohydrate (Molisch test), and was retained. The red, acid hydrolysates and the washings were combined (1·5 l.), and barium carbonate (70 g.) was added with stirring. When reaction had ceased, the mixture was centrifuged and the supernatant liquor (*ca.* pH 2) evaporated to *ca.* 500 c.c. Addition of ethanol (1 l.) produced a white precipitate (P) which was isolated on the centrifuge, then reprecipitated with ethanol from aqueous solution, washed with ethanol and ether, and dried (1·2 g.).

The supernatant liquor from the isolation of (P) was concentrated to *ca.* 400 c.c. and neutralised with barium carbonate. The mixture was centrifuged, and evaporation of the supernatant liquor gave a neutral brown syrup (10·6 g.), in which the following reducing sugars were detected by paper chromatography: galactose, glucose, arabinose, xylose (main components), rhamnose, fucose, compounds with R_{Rh} 1·25 and 1·31 in (*b*) [(A) and (B) respectively, see below], hexuronic acid, and oligosaccharides (minor components). Considerable amounts of amino-acids (located with ninhydrin) were also present.

Residue (R) was further heated with acid (2 × 250 c.c.; 3 hr. each time), but addition of ethanol (300 c.c.) to the concentrated hydrolysate (150 c.c.) produced only a slight precipitate, which was not further examined. After evaporation of the ethanol, the solution was neutralised as before, the solids were removed on the centrifuge, and the supernatant liquor was concentrated. The resultant syrup (0·6 g.) contained xylose (mainly), with galactose, glucose, arabinose, and acidic oligosaccharides.

An aqueous solution of the combined monosaccharide-containing syrups was passed successively through columns of IR-120(H) and IRA-400(CO_3) resin, then the column effluent, after concentration to *ca.* 200 c.c., was allowed to percolate through a squat charcoal column [5] (diam. 10 cm., length 4 cm.) which had been previously washed with ethanol and water. Elution of the column with water (1·5 l.) afforded a fraction (3·3 g.) containing galactose, glucose, arabinose, xylose, and rhamnose, and much smaller amounts of fucose and mannose. Further elution with alcohol–water gave mixtures of compounds (A) and (B), and of oligosaccharides (0·8 g.). Hydrolysis of the latter yielded a mixture (0·66 g.) consisting mainly of galactose, glucose, arabinose, and xylose.

Examination of Acidic Mono- and Oligo-saccharides.—Treatment of the IRA-400(CO_3) resin used in the above purification with excess of N-sulphuric acid, followed by washing with water, gave a solution which after neutralisation (as above), filtration, and evaporation yielded a white solid (2·7 g.) which apparently contained small amounts of at least three aldobiouronic acids, with higher oligosaccharides. Cations were removed from the mixture on IR-120(H) resin, and the remaining material hydrolysed with 2N-acid. Passage of the hydrolysate through an IR-4B(OH) resin column and evaporation of the effluent gave a syrup (0·2 g.) containing galactose, glucose, xylose, and rhamnose. The resin column was then eluted with 0·1N-sulphuric acid until carbohydrate was no longer displaced (Molisch test). The acid effluent was neutralised as before, filtered, passed through IR-120(H) resin, and evaporated. The resultant syrup

[13] Hough, Jones, and Wadman, *J.*, 1956, 1702.

XUM

(0·2 g.) consisted mainly of hexuronic acid and acidic oligosaccharides, but glucurono-6 ⟶ 3-lactone and mono-*O*-methylhexuronic acid (both recognised by chromatographic behaviour) were also present. Chromatographic separation on paper sheets with solvent (*a*) gave hexuronic acid (30 mg.), a mixture of acidic oligosaccharides (80 mg.), glucurono-6 ⟶ 3-lactone (<5 mg.), and mono-*O*-methylhexuronic acid (<5 mg.). Hydrolysis of the acidic oligosaccharides with 2N-acid for 18 hr. gave rhamnose, galactose, and hexuronic acid; glucurono-6 ⟶ 3-lactone was not detected.

The hexuronic acid fraction (30 mg.) was converted into methyl ester methyl glycoside by heating it under reflux for 18 hr. in methanolic hydrogen chloride (2% w/w), and the isolated product was reduced with potassium borohydride (20 mg.) in water (2 c.c.). After 2 hr., 2N-sulphuric acid (3 c.c.) was added, then the solution was heated at 100° for 6 hr., passed through IR-120(H) and IRA-400(CO_3) resins, and evaporated, yielding a syrup (12 mg.) containing galactose and glucose (*ca.* 3 : 1). Crystallisation from methanol gave D-galactose, m. p. and mixed m. p. 162—164°.

Examination of Precipitate (*P*).—After drying, this material (1·2 g.) dissolved only partially in water, giving a solution with an acid reaction. Hydrolysis (16 hr.), followed by paper chromatography, indicated that hexuronic acid was the main monosaccharide constituent, but xylose and traces of galactose and rhamnose were also present. A dispersion of the material in water, after adjustment to *ca.* pH 5 with sodium hydroxide, was treated with a pectinase preparation at 37°. After 5 days, undissolved material was isolated on the centrifuge, and hydrolysed (16 hr.) with acid. The combined acid and enzyme hydrolysates were neutralised with barium carbonate, cations were removed on IR-120(H) resin, then evaporation of the solution gave a syrup (0·7 g.) consisting of hexuronic acid (mainly), acidic oligosaccharides, and xylose; glucurono-6 ⟶ 3-lactone was not detected. Fractionation on paper chromatograms, with solvent (*a*), gave xylose (25 mg.) and a fraction (0·4 g.) containing acidic mono-, di-, and tri-saccharides. The last fraction was converted into methyl ester methyl glycoside by heating it under reflux for 16 hr. in methanolic hydrogen chloride (2% w/w; 50 c.c.). Reduction of the product with potassium borohydride (130 mg.) in water (5 c.c.) for 20 hr. at 2°, followed by hydrolysis and passage through IR-120(H) and IRA-400(CO_3) resins, afforded D-galactose (190 mg.) which after crystallisation from methanol had m. p. and mixed m. p. 163—164° and $[\alpha]_D$ +80° (equil. value; *c* 1·0).

Separation and Characterisation of Neutral Monosaccharides.—The several neutral monosaccharide fractions isolated from the plum-leaf hydrolysates as above were combined (4·4 g.), and the sugars converted into their di-*O*-*iso*propylidene derivatives (4·1 g.) by the action of acetone (100 c.c.) and concentrated sulphuric acid (5 c.c.) on the powder produced by evaporating an aqueous solution of the sugars in the presence of Celite (10 g.).[4] The *O*-*iso*propylidene compounds were dissolved in 0·1N-sulphuric acid (15 c.c.), and the solution was kept at 20° for 6½ hr. Anions were then removed on IR-4B(OH) resin, and the resultant solution shaken with chloroform (equal vol.; 4 times). Hydrolysis, by 0·5N-acid for 1 hr., of the chloroform-soluble *O*-*iso*propylidene compounds afforded a mixture (1·3 g.) of mainly galactose and arabinose, with small amounts of xylose and fucose. The *O*-*iso*propylidene compounds from the aqueous layer gave, on hydrolysis as before, a mixture (1·2 g.) of glucose and xylose, together with small amounts of arabinose and rhamnose.

Portions of these mixtures were fractionated on large paper sheets, solvents (*b*) and (*c*) being used. The sugars were eluted from the appropriate parts of the chromatograms with cold water, and the solutions so obtained were passed through IR-120(H) and IRA-400(CO_3) resins before evaporation to dryness. Eventually the following monosaccharides were obtained: (i) D-Galactose. Crystallisation of the syrup (200 mg.), $[\alpha]_D$ +75° (*c* 2·0), from methanol–ethanol afforded α-D-galactose (150 mg.), m. p. and mixed m. p. 164—165°, $[\alpha]_D$ +115° (5 min.) ⟶ +81° (equil. value; *c* 1·5). (ii) D-Glucose. The syrup (300 mg.) with $[\alpha]_D$ +45° (*c* 3·0) contained a little galactose and xylose, but partly crystallised; trituration with methanol gave α-D-glucose (40 mg.), m. p. and mixed m. p. 148°, $[\alpha]_D$ +97° (10 min.) ⟶ +51° (equil. value; *c* 0·5). The remaining material was heated under reflux in methanolic hydrogen chloride (1% w/w) for 16 hr. and yielded methyl α-D-glucopyranoside (110 mg.), m. p. and mixed m. p. 165—166°, $[\alpha]_D$ +160° (*c* 1·0). (iii) L-Arabinose. The sugar (360 mg.) crystallised spontaneously, and recrystallisation from methanol–ethanol gave L-arabinose (255 mg.), m. p. and mixed m. p. 159—160°, $[\alpha]_D$ +101° (equil. value; *c* 1·8). (iv) D-Mannose. Paper-chromatographic examination of the material in the mother-liquors from the crystallisation

of arabinose indicated the presence of small amounts of mannose and fructose in addition to arabinose, the first two of these sugars not being separated from each other (fructose was detected with orcinol–trichloroacetic acid). For the isolation of mannose, the mixture was heated in N-acid for 2 hr., to destroy the hexulose. Sheet-paper chromatography [solvent (*b*)] of the product, in which fructose was not detected, yielded syrupy D-mannose (14 mg.), $[\alpha]_D$ +12° (*c* 0·7). The derived phenylhydrazone had m. p. and mixed m. p. 188° (decomp.). (v) D-Xylose. A fraction (120 mg.) in which xylose was the main component had $[\alpha]_D$ +18° (*c* 1·2). Crystallisation from methanol–acetone afforded α-D-xylose (80 mg.), m. p. and mixed m. p. 146—147°, $[\alpha]_D$ +75° (3 min.) ⟶ +18° (equil. value; *c* 1·6). The mother-liquors contained xylose and a little arabinose, the mixture having $[\alpha]_D$ +35° (*c* 1·2). (vi) L-Rhamnose. Crystallisation of a rhamnose-containing fraction (40 mg.) from ethanol–acetone gave α-L-rhamnose monohydrate (20 mg.), m. p. and mixed m. p. 94—96°, $[\alpha]_D$ +8° (equil. value; *c* 0·9). (vii) L-Fucose. The above chromatographic separations yielded a fraction (33 mg.) containing fucose and xylose (*ca.* 1 : 1). To facilitate its characterisation, more fucose was isolated later during charcoal chromatography of larger quantities of plum-leaf monosaccharides for the isolation of (A) and (B). Then crystallisation from methanol–acetone afforded α-L-fucose, m. p. and mixed m. p. 143—144°, $[\alpha]_D$ −71° (equil. value; *c* 3·3).

Isolation of Compounds (A) and (B) (with J. D. Anderson).—Fractionation of the monosaccharide mixture from 37 g. of alcohol-insoluble plum leaf residue yielded insufficient of (A) and (B) for their characterisation. Accordingly further preparations were carried out, the following being typical: Alcohol-insoluble plum-leaf residue (350 g.) was heated with acid (5 l.), the resultant solution was brought to pH 7 with sodium hydroxide, and the bulk of the sodium sulphate removed by concentration of the solution and addition of methanol. Enrichment of (A) and (B) was effected by addition of acetone to a concentrate of the methanolic liquors, the ensuing precipitate being discarded. The product (12·5 g.) was fractionated on a squat charcoal column,[5] previously washed with water, by stepwise elution with water followed by water–ethanol mixtures. Water containing 1% of ethanol eluted a mixture (1·2 g.) of galactose, arabinose, xylose, rhamnose, and fucose; 2·5% ethanol eluted a fraction (305 mg.) which contained most of the compound (A) and some fucose; 5% ethanol eluted a fraction (120 mg.) containing (B). All of the fractions were contaminated with other substances; in those fractions containing (A) and (B) non-reducing material was also present which on hydrolysis (3 hr.) gave galactose, glucose, and arabinose in small amounts.

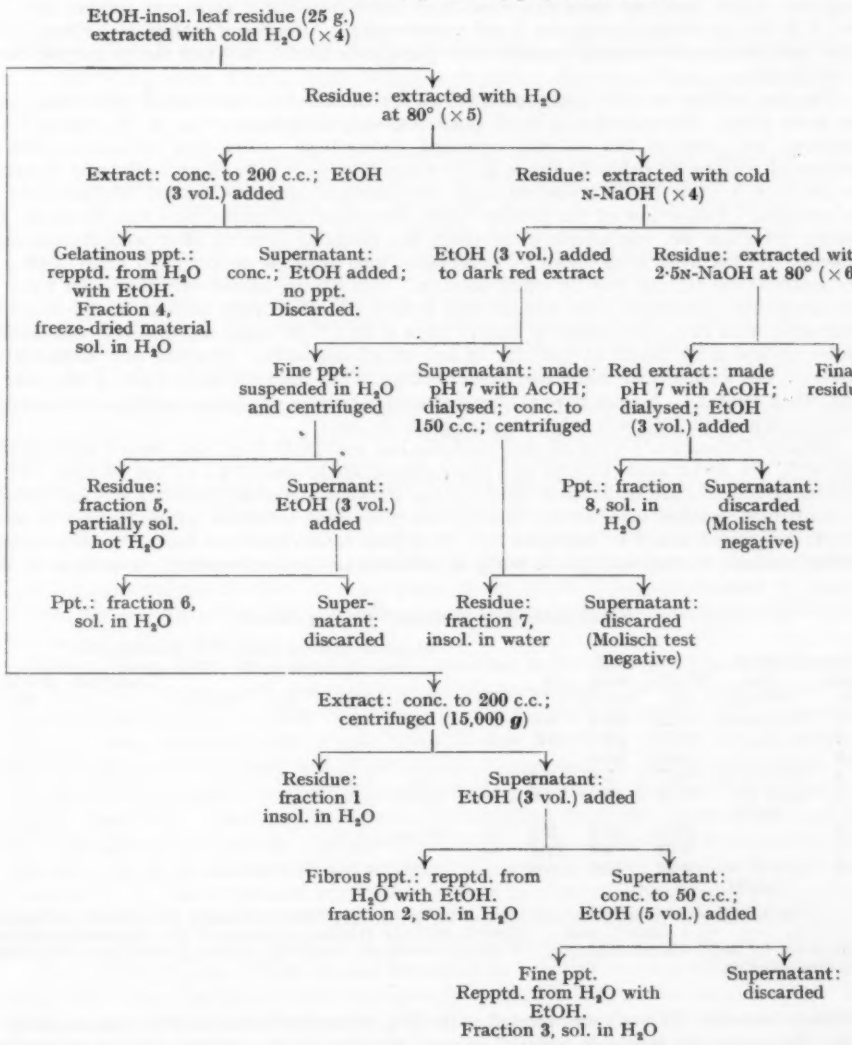
Characterisation of Compound (A) as 2-O-*Methyl*-D-*xylose*.—For the purification of (A), the material in appropriate fractions of charcoal-column effluent was heated with acid (3 hr.) which was then removed on IR-4B(OH) resin, and the products were submitted to chromatography on paper sheets with solvent (*c*). The compound was then eluted from the paper with cold water, and the solution passed through IR-120(H) and IRA-400(CO_3) resins and evaporated. The resultant colourless syrup (yield, *ca.* 20 mg. per 100 g. of dry alcohol-insoluble leaf residue) gave crystalline (A), which after recrystallisation from acetone had m. p. 132—133° (Kofler block), $[\alpha]_D$ +37° ± 6° (equil. value; *c* 0·3), R_{Rh} 1·33, 1·25, and 1·22 in solvents (*a*), (*b*), and (*c*) respectively, thus resembling a mono-*O*-methylpentose (Found: OMe, 17·9. Calc. for $C_5H_9O_4$·OMe: OMe, 18·9%). De-*O*-methylation [13] of the compound (2 mg.) was achieved by treatment with hydrobromic acid (48% w/v) at 100° for 4 min. Paper-chromatography of the neutralised (Ag_2CO_3) products indicated the presence of xylose. Quantitative estimation [14] of the formaldehyde liberated on oxidation of the compound (1·00 mg.) with sodium metaperiodate in the presence of sodium hydrogen carbonate gave 90, 148, and 184 μg. after 1·5, 3·3, and 24 hr. respectively, corresponding to yields of 0·49, 0·81, and 1·00 mole formaldehyde per mole of mono-*O*-methylpentose. The compound was indistinguishable on the paper chromatogram from 2-*O*-methylxylose, which gave a red colour with *p*-anisidine hydrochloride, but distinguishable from the 3-*O*-methyl derivative, which gave a red-brown colour and had R_{Rh} 1·38, 1·30, and 1·25 in (*a*), (*b*), and (*c*) respectively. Characterisation of (A) as 2-*O*-methyl-D-xylose was confirmed by a mixed m. p. determination (133—135°) with an authentic sample, and a comparison of their *X*-ray powder photographs. Specimens of 2- and 3-*O*-methyl-D-xylose were kindly supplied by Dr. G. O. Aspinall.

Characterisation of Compound (B) as 2-O-*Methyl*-L-*fucose*.—A fraction eluted from charcoal with 5% ethanol partly crystallised, and trituration with acetone afforded crystalline (B) (5 mg.). Paper chromatography of the rest of this fraction, and of similar fractions, gave products from

[14] Hough, Powell, and Woods, *J.*, 1956, 4799.

which further small amounts of crystalline (B) were obtained only with difficulty; crystallisation appeared to be hindered by material which was non-reducing and not held on ion-exchange resins. The crystalline sugar, the yield of which was roughly 5 mg. per 100 g. of dry alcohol-insoluble leaf residue, had m. p. 149—150°, $[\alpha]_D$ −75° ± 4° (equil. value; *c* 0·5) and R_{Rh} 1·46, 1·31, and 1·38 in (*a*), (*b*), and (*c*) respectively, suggestive of a deoxymono-*O*-methylhexose (Found OMe, 17·5. Calc. for $C_6H_{11}O_4$·OMe: OMe, 17·4%). De-*O*-methylation [13] with hydrobromic acid

Fractional extraction of plum-leaf polysaccharides.


EtOH-insol. leaf residue (25 g.) extracted with cold H₂O (×4)
Residue: extracted with H₂O at 80° (×5)
Extract: conc. to 200 c.c.; EtOH (3 vol.) added
Residue: extracted with cold N-NaOH (×4)
Gelatinous ppt.: repptd. from H₂O with EtOH. Fraction 4, freeze-dried material sol. in H₂O
Supernatant: conc.; EtOH added; no ppt. Discarded.
EtOH (3 vol.) added to dark red extract
Residue: extracted with 2·5N-NaOH at 80° (×6)
Fine ppt.: suspended in H₂O and centrifuged
Supernatant: made pH 7 with AcOH; dialysed; conc. to 150 c.c.; centrifuged
Red extract: made pH 7 with AcOH; dialysed; EtOH (3 vol.) added
Final residue
Residue: fraction 5, partially sol. hot H₂O
Supernant: EtOH (3 vol.) added
Ppt.: fraction 8, sol. in H₂O
Supernatant: discarded (Molisch test negative)
Ppt.: fraction 6, sol. in H₂O
Super-natant: discarded
Residue: fraction 7, insol. in water
Supernatant: discarded (Molisch test negative)
Extract: conc. to 200 c.c.; centrifuged (15,000 g)
Residue: fraction 1 insol. in H₂O
Supernatant: EtOH (3 vol.) added
Fibrous ppt.: repptd. from H₂O with EtOH. fraction 2, sol. in H₂O
Supernatant: conc. to 50 c.c.; EtOH (5 vol.) added
Fine ppt. Repptd. from H₂O with EtOH. Fraction 3, sol. in H₂O
Supernatant: discarded

(48% w/w) for 9 min. at 100°, followed by paper chromatography, indicated that fucose was the parent sugar. Comparison of (B) on paper chromatograms with authentic samples of 2- and 3-*O*-methyl-L-fucose [the latter having R_{Rh} 1·29 and 1·13 in solvents (*a*) and (*b*) respectively], kindly supplied by Dr. Elizabeth Percival, suggested identity with the former. Further

evidence for location of the *O*-methyl group at position 2 was obtained by periodate oxidation of the sugar (0·9 mg. samples) at pH 5·0 both before and after reduction *in situ* with sodium borohydride, and Warburg estimation of the carbon dioxide liberated (Found: 1·08 and 0·20 mol. respectively). 2-*O*-Methyl-L-rhamnose gave similar results (Found: 1·10 and 0·20 mol. respectively).[15] Identity of (B) as 2-*O*-methyl-L-fucose was confirmed by its m. p. (149—150°) when admixed with an authentic sample (m. p. 149—150°), and the identity of *X*-ray powder photographs.

Fractional Extraction of Plum-leaf Polysaccharides.—The procedure is detailed in the flow diagram. Eight fractions were extracted from alcohol-insoluble plum-leaf residue (25 g.). Nos. 1, 3, and 5—8 were brown, nos. 2 and 4 were white. After being washed with ethanol and ether, and dried under reduced pressure over phosphoric oxide, they had the properties listed in the Table.

The final residue (see flow diagram), a brown fibrous material, was washed with water until free from alkali. Hydrolysis of a small portion gave glucose and xylose (3 : 1), with a little arabinose, but most of the material remained undissolved. After two extractions with a solution of sodium hypochlorite (*ca.* 2 g.) in water (100 c.c.), containing acetic acid to bring the pH to 4, a white product was obtained; no carbohydrate was detected (Molisch test) in the extracts. Extraction of the product with 2N-sodium hydroxide gave two fractions (9*a* and *b*). Fraction (9*a*) was soluble in 2N-alkali, but insoluble in water after precipitation with ethanol. It was freed from alkali by washing it with aqueous alcohol, and dried (0·09 g.). The material was stained blue by iodine solution. After being heated with N-acid for 8 hr., it was apparently unchanged, but glucose and a trace of xylose were present in the solution. Hydrolysis with 72% w/w sulphuric acid (7 days at 20°),[16] in which the material was readily soluble, followed by N-acid at 100° for 16 hr., afforded glucose. Fraction (9*b*), insoluble in 2N-alkali, was washed with water and dried (0·13 g.). The material did not give a blue colour with iodine solution. No sugars were liberated when a portion was heated with N-acid for 8 hr., but treatment with 72% w/w sulphuric acid gave glucose.

Cellulose Estimation.[11]—The alcohol-insoluble leaf residue (0·75 g.) was heated under reflux with 80% v/v acetic acid (15 c.c.) and concentrated nitric acid (1·5 c.c.) for 20 min. After dilution of the mixture with water (50 c.c.), the insoluble cellulosic material was isolated on the centrifuge, washed with water, ethanol, and ether, and air-dried (yield, 74 mg.) (Found: N, 1·2; sulphated ash, 3·4; H_2O, 5·2%). This yield after correction for ash, moisture, and protein content, corresponds to *ca.* 8·5% of cellulose in the leaf residue. A portion of the

Fractionation of plum-leaf polysaccharides.

Fraction no.	Extraction solvent	Weight (g.)	Sulphated ash (%)	N (%)	Monosaccharides detected in hydrolysates [a]						
					Gal	Glu [b]	Arab	Xyl	Rhamn	Gal'uronic-A	2-*O*-Me-Xyl
1	Cold water	0·22	27·4	5·8	t	—	t	—	—	—	—
2	,,	0·17	22·7	Nil	+++	—	++	—	+	+	t
3	,,	1·22	81·0		—	—	—	—	—	—	—
4	Hot water	0·57	5·5	0·2	++	+	+++	+	t	+	t
5	Cold N-NaOH	0·20	35·2	2·9	—	+++	t	+	—	t	—
6	,,	3·61	56·4	3·0	+	+++	++	++	t	t	—
7	,,	0·63	4·5	12·2	—	—	—	—	—	—	—
8	Hot 2·5N-NaOH	0·34	12·3	0·6	+	++	+++	+++	+	+	t

[a] Each fraction was hydrolysed for 8 hr. and the hydrolysates neutralised with barium carbonate; +++, ++, +, t (trace), and — (absent) indicate relative amounts of the monosaccharides as detected by paper chromatography. [b] All the fractions containing glucose gave a blue colour with iodine solution.

cellulosic material (37 mg.) was treated with 72% w/w sulphuric acid (0·5 c.c.) as above.[16] After the hydrolysis, insoluble material (8 mg.) was filtered off, and the solution neutralised with barium carbonate and concentrated to a small volume. Paper chromatography indicated that glucose was the only sugar present apart from a trace of xylose, and the optical rotation

[15] Hough and Woods, *Chem. and Ind.*, 1957, 1421.
[16] Monier-Williams, *J.*, 1921, **119**, 803.

XUM

of the solution was equivalent to that of a similar solution of D-glucose (20 mg.). On this basis the cellulosic material was calculated to contain at least 49% of cellulose which corresponds to 4·8% of cellulose in the leaf residue.

We thank the Agricultural Research Council for the award of a Fellowship (to P. A.) and Dr. T. Bevan for the *X*-ray powder photographs.

THE UNIVERSITY, BRISTOL. [*Received, July 8th,* 1958.]

---

904. *The Biosynthesis of Polysaccharides. Part II.*[1] *Incorporation of* $^{14}CO_2$ *into Plum-leaf Polysaccharides during Photosynthesis.*

By P. ANDREWS and L. HOUGH.

The rate of incorporation of $^{14}CO_2$ into plum leaves during 48 hours' photosynthesis and the distribution of the ^{14}C between the methanol-soluble and -insoluble portions of the leaves, were determined. At the end of this period the polysaccharides in the insoluble portion were fractionated and the specific activities of their main monosaccharide constituents estimated. ^{14}C-Labelled D-glucose, D-galactose, L-rhamnose, L-arabinose, D-xylose, and D-galacturonic acid were obtained crystalline or as crystalline derivatives. The extent of ^{14}C incorporation into these monosaccharides varied widely from one to another, and the specific activities of each monosaccharide, except D-galactose, differed significantly in different polysaccharide fractions.

IN Part I,[1] the polysaccharide constituents of Victoria plum leaves were shown to consist of appreciable quantities of D-galactose, L-arabinose, D-xylose, L-rhamnose, and D-galacturonic acid, in addition to D-glucose. In a tracer experiment, Hough and Pridham[2] observed the incorporation of $^{14}CO_2$ into these units during photosynthesis, suggesting the existence of a dynamic equilibrium between the polysaccharides and their monosaccharide precursors. Since the majority of plant polysaccharides contain one or more of these monosaccharides, which may well be preformed in the leaves for their subsequent inclusion into polysaccharides in other parts of the plant, it was of interest to examine further the assimilation of $^{14}CO_2$ by plum leaves, particularly the appearance of ^{14}C in the constituent polysaccharides.

Mature leaves from Victoria plum trees were kept in the dark for 24 hr. to deplete their polysaccharide content and then allowed to photosynthesise in the presence of $^{14}CO_2$. The leaves were placed initially in a closed system[3] containing 5% of $^{14}CO_2$, only traces of which were recovered after 6 and 8 hours' photosynthesis by the leaves under the illumination provided (about 400 foot-candles). Incorporation and metabolism of $^{14}CO_2$ was allowed to proceed for periods varying from 1 to 48 hr., but in those experiments of more than 8 hr. duration the leaves were removed from the closed system at that time and allowed to continue photosynthesis in the open. Considerable differences have been observed in the photosynthetic activities of apple leaves;[4,5] therefore in an attempt to minimise the effects of such variations in our experiments, about twenty plum leaves were selected each time and the conditions for photosynthesis were standardised as far as possible. However, some variation in the total weights of the leaves was unavoidable.

The leaf-blades were broken up and immediately dropped into hot ethanol to halt their metabolism, then the pieces were exhaustively extracted with methanol and ether. The extracts and the insoluble leaf residues from each experiment were assayed in order to determine the overall distribution of ^{14}C in the leaves after various intervals. At all

[1] Part I, Andrews and Hough, preceding paper.
[2] Hough and Pridham, *Nature*, 1956, **177**, 1039.
[3] Livingston and Medes, *J. Gen. Physiol.*, 1947, **31**, 75.
[4] Heinicke, Agric. Expt. Station, Cornell, Bull. No. 577, 1933.
[5] Asselbergs, *Plant Physiol.*, 1957, **32**, 326.

times the extracts contained more of the original $^{14}CO_2$ activity than did the insoluble leaf residue (Table 1). The activity in the extracts was the first to reach a maximum, which,

TABLE 1. *^{14}C in leaf fractions, as percentage of ^{14}C supplied in $^{14}CO_2$.*

Period of photosynthesis (hr.)	1	1·5	3	6	15·5	24	48
Activity in leaf extract	18·4	24·5	53·8	58·4	56·3	52·3	49·0
Activity in insoluble leaf residue ...	6·2	9·5	25·0	39·9	40·7	38·7	32·3
Total activity in leaves	24·6	34·0	78·8	98·3	97·0	91·0	81·3

from a plot of the figures, seemed to occur after about 5 hours' photosynthesis. A less marked maximum in the activity in the leaf residues was attained after 8—10 hr. After reaching their maxima both curves showed a gradual and parallel decline. Over 98% of the initial $^{14}CO_2$ activity was accounted for in the two leaf fractions after photosynthesis for 6 hr., and the following loss of activity may well have been due to the translocation of labelled compounds into the stems.[6]

TABLE 2. *Relative distribution of ^{14}C between leaf fractions.*

Period of photosynthesis (hr.)	1	1·5	3	6	15·5	24	48
Leaf extracts (%)	75	72	68	59·5	58	57·5	60
Insoluble leaf residue (%)	25	28	32	40·5	42	42·5	40

In the early stages the proportion of ^{14}C in the leaf extracts greatly exceeded that in the insoluble residue (Table 2), but that in the latter quickly increased, so that after 6 hr., when a steady state was reached, about 40% of the total activity assimilated by the leaves then resided in this fraction. Thereafter the proportion rose very slowly to 42·5% after 24 hr. and gradually diminished to 40% again during the next 24 hr. These results are consistent with a rapid initial incorporation of the ^{14}C into sugar phosphates and other compounds of low molecular weight, and their subsequent use in macromolecular synthesis. The rate of appearance of ^{14}C in the leaf residue may have been accelerated especially in the early stages by factors consequent on the pre-starvation of the leaves, which would have depleted their total carbohydrate content, and the high initial carbon dioxide concentration. However, since the total activity in the leaf residues never exceeded that in the extracts, in fact it decreased slowly after reaching a maximum, the macromolecular substances as a whole are clearly not accumulated as end-products of the leaf metabolism. Their constituent units are probably further redistributed by participation in the biological processes in the leaf.

From a knowledge of the specific activities involved, values were calculated for the percentage of the carbon in the insoluble leaf residues which had originated from $^{14}CO_2$. In order to compare these values one with another, allowance was now made for the variations in the quantity of leaves used in different experiments by adjusting each value to accord with a weight of 3 g. for the insoluble leaf residue. The values so obtained (Table 4) lay on a curve which rose rapidly to a maximum value of about 3·4% after 9 hours' photosynthesis and then declined slowly.

To obtain information on the extent of ^{14}C incorporation into the monosaccharide constituents of the various leaf polysaccharides after photosynthesis for 48 hr., the appropriate insoluble leaf residue was extracted[1] successively with hot water and cold and hot sodium hydroxide solution. The three polysaccharide fractions so obtained were hydrolysed separately, and the components of the resultant monosaccharide mixtures isolated by paper chromatography. Further purification of those sugars obtained in quantities (>2 mg.) considered sufficient for accurate assay was effected with ion-exchange resins, then each monosaccharide was diluted with the appropriate inactive monosaccharide, crystallised, and assayed. The results were confirmed by the preparation and assay of various derivatives of the sugars (Table 5). In order to relate these figures with those in Table 4, the corresponding values for the percentage of sugar-carbon

[6] Nelson and Gorham, *Canad. J. Bot.*, 1957, **35**, 340, 704.

originating from the $^{14}CO_2$ were calculated, again on the basis of 3 g. of insoluble leaf residue (Table 3).

TABLE 3. *Sugar-carbon (%) originating from* $^{14}CO_2$ *after 48 hours' photosynthesis.*

	Water-soluble polysaccharides	Polysaccharides soluble in cold N-NaOH	Polysaccharides soluble in hot 2·5N-NaOH
D-Glucose	—	21·6	18·5
D-Galactose	1·66	—	1·72
L-Rhamnose	0·94	—	1·12
L-Arabinose	1·58	0·90	0·74
D-Xylose	0·21	0·30	0·49
D-Galacturonic acid	0·08	—	—

Whilst the incorporation of isotopic carbon into the D-glucose of plum-leaf polysaccharides greatly predominated, significant activity was determined in D-galactose, L-rhamnose, L-arabinose, D-xylose, and D-galacturonic acid. Hough and Pridham's observations [2] are therefore confirmed, in that all these monosaccharides have acquired different specific activities. However, fractionation of the leaf polysaccharides has shown that the specific activities of the various component monosaccharides differed from one fraction to another, thus revealing a hitherto unsuspected complexity (cf. Perlin [7]). The incorporation of ^{14}C into leaf starches during photosynthesis of the leaves in $^{14}CO_2$ has been studied,[8] but similar aspects of the biological synthesis of other leaf polysaccharides have received little attention. Ginsburg and Hassid [9] isolated uniformly ^{14}C-labelled xylose and arabinose from canna-leaf polysaccharides, and Cowie and Krotkov [10] similarly obtained these labelled pentoses, together with ^{14}C-labelled galactose, from wheat seedlings.

The high specific activity of D-glucose is consistent with the important rôle of starch in leaf metabolism, as was suggested by the observations of Vittorio, Krotkov, and Reed,[8] who showed that, during photosynthesis, ^{14}C from $^{14}CO_2$ appeared in the starch fraction of tobacco leaves, previously stored in the dark, more rapidly than it did in the free glucose, fructose, and sucrose. In contrast, the very small amount of ^{14}C now found in D-galacturonic acid suggests that pectic acid is not at all an active metabolite in mature plum leaves. Both D-galactose and L-arabinose attained considerably higher specific activities than did D-galacturonic acid. Therefore if L-arabinose arises from D-galactose by oxidative decarboxylation *via* D-galacturonic acid, as has been suggested by isotopic tracer studies,[11] the intermediary hexuronic acid seems to be decarboxylated, or otherwise metabolised, without being incorporated to any great extent into the pectic acid.

EXPERIMENTAL

Determination of ^{14}C *Activities.*—Activities were determined in a Geiger counter with a thin mica end-window. For estimation of the activities of crystalline ^{14}C-labelled compounds and insoluble leaf residues, samples (usually 6—12 mg.) were burnt in a stream of oxygen, the $^{14}CO_2$ produced was passed into hot barium hydroxide solution (saturated at 20°), and the precipitated $Ba^{14}CO_3$ collected in layers (*ca.* 20 mg./cm.^{2}, equivalent to infinite thickness for counting), which were washed with water and dried at 120° before being used for activity measurements. Sufficient counts were taken to give a standard error of count of $\pm 3\%$ or better. The counting equipment was calibrated in terms of $Ba^{14}CO_3$ by determining the count-rate of infinitely thick layers of $Ba^{14}CO_3$ prepared from poly([^{14}C]methyl methacrylate) of known specific activity (supplied by the Radiochemical Centre, Amersham). A disc of this polymer was used as a standard reference source.

The ^{14}C activities of solutions (*e.g.*, alcohol extracts of leaves) were determined by infinite

[7] Perlin, *Canad. J. Chem.*, 1958, **36**, 810.
[8] Vittorio, Krotkov, and Reed, *Science*, 1954, **119**, 906; Gibbs, *Plant Physiol.*, 1951, **26**, 549; Gibbs and Kandler, *Proc. Nat. Acad. Sci. U.S.A.*, 1957, **43**, 446.
[9] Ginsburg and Hassid, *J. Biol. Chem.*, 1956, **223**, 277.
[10] Cowie and Krotkov, *Canad. J. Bot.*, 1957, **35**, 1.
[11] Neish, *Canad. J. Biochem. Physiol.*, 1955, **33**, 658; Seegmiller, Axelrod, and McCready, *J. Biol. Chem.*, 1955, **217**, 765; Seegmiller, Jang, and Mann, *Arch. Biochem. Biophys.*, 1956, **61**, 422.

thinness counting, for which the samples were prepared by pipetting aliquot parts (usually 5—20 μl.) on to nickel planchettes and evaporating the solvent at 120°. Sample weights were kept below *ca.* 0·2 mg. whenever possible, having regard also to the counting-rates. The variations in the results indicated an overall statistical and sample-preparation error of ±5% in most cases, but up to ±10% on the least active samples. The counting equipment was calibrated for this method of measurement with weighed aliquot parts (2—12 μl.) from a solution (1 c.c.) containing [6-^{14}C]glucose (50 μc; 1·2 mg.).

Apparatus for Photosynthetic Experiments.—Steady illumination was provided in an apparatus similar to that described by Folkes, Willis, and Yemm.[12] It consisted of an iron frame supporting, at the top, twelve 150 w tungsten-filament lamps mounted between a reflecting surface above and a glass-bottomed water tank below. The tank was fitted with a constant-level device, and the water passing through it conducted away heat from the electric lamps. Fans maintained a circulation of air through the apparatus, and the photosynthetic chamber was placed on a wooden stage which could be raised and lowered beneath the water tank. To adapt the apparatus for rearing plants in the laboratory, an automatic switch was put in circuit with the lamps to vary the illumination periods.

The photosynthetic chamber [3, 8] was a desiccator (vol. 4 l.) with two inlet tubes, both with stopcocks, passing through the centre of the lid. One inlet tube was terminated immediately inside the lid, and the other extended to within *ca.* 1 cm. of the bottom of the desiccator. Small beakers containing water, for holding leaves, were disposed around the shelf of the desiccator and held in place with a metal frame. A small beaker containing $Ba^{14}CO_3$ was placed in the bottom of the desiccator, to surround the end of the long inlet tube; sulphuric acid (30% v/v) was also put in the bottom for humidity control.

Procedure for Photosynthetic Experiments.—For each experiment four spurs, each bearing four or five leaves of length 7—10 cm. were cut from a plum tree (*Prunus domestica* var. Victoria) in early September 1956, and kept for 24 hr. in the dark with the cut ends of the stems in water. With the spurs in position in the desiccator, the pressure inside was reduced through the short inlet tube by *ca.* 6 cm. of Hg, then lactic acid solution (80% v/v) was added through the long inlet tube to the $Ba^{14}CO_3$ in the beaker at the bottom. In each experiment, *ca.* 9 mmoles (1·77 g.) of $Ba^{14}CO_3$ were used, this being enough to give an initial $^{14}CO_2$ concentration in the desiccator of 5%; the specific activity varied from 7 to 23 μc/mmole in different experiments. Sufficient lactic acid (*ca.* 25 c.c.) was used to immerse the lower end of the long inlet tube by 1 cm. When the evolution of $^{14}CO_2$ had ceased, the desiccator was placed under the light battery and the pressure inside adjusted to atmospheric by the admission of air through the long inlet tube. The stopcock on this tube was then left open to the air, loss of $^{14}CO_2$ being prevented by the immersion of the lower end of the tube in lactic acid.

Trials showed that, with the above experimental array, the intensity of illumination received by the leaves in the desiccator was about 400 foot-candles (measured with a Weston Photronic foot-candle meter), and that they incorporated the $^{14}CO_2$ in 6—8 hr. Accordingly at the end of photosynthesis periods of less than 8 hr., or after 8 hr. when longer periods were required, the desiccator was swept out for 10 min. with a rapid stream of carbon dioxide-free air, and any carbon dioxide present was trapped in sodium hydroxide solution. Not more than 2% of the activity supplied was recovered as $^{14}CO_2$ after any of the 6 and 8 hr. periods. In cases where photosynthesis was to be for more than 8 hr. the spurs were removed from the desiccator at that time and left under the light battery with the cut ends of the stems still in water for the remainder of the time. Only very slight activity was detected in this water in any of the experiments. The illumination intensity received in the open was about 500 foot-candles.

Each experiment was concluded by rapidly breaking up the leaves and immediately dropping the leaf-blades into boiling ethanol. Then the pieces were transferred to a Soxhlet apparatus and extracted successively with methanol and ether. The ethanol, methanol, and ether extracts from each experiment were combined; after radioactivity determinations the resultant solutions were evaporated to dryness and the residues retained for further investigation. The insoluble leaf residues were dried at 60°, powdered, and finally dried to constant weight (Found: C, 43·3%) over phosphoric oxide before radioactivity determinations. The results are summarised in Table 4.

Isolation of ^{14}C-Labelled Monosaccharides from Plum-leaf Polysaccharides.—The polysaccharides in the insoluble leaf residue from the 48 hr. experiment were extracted by successive

[12] Folkes, Willis, and Yemm, *New Phytol.*, 1953, **51**, 317.

treatments with hot water, N-sodium hydroxide at 20°, and 2·5N-sodium hydroxide at 80°, the extraction with each solvent being repeated (4—6 times) until no further material was dissolved. The final insoluble residue (217 mg.; 2·4 μc) was retained for further investigation. The aqueous extract was concentrated, and the alkaline extracts neutralised with acetic acid, then the polysaccharides in each extract were precipitated with ethanol. The crude polysaccharide fractions were washed several times with hot methanol, then dissolved in N-sulphuric acid, and the solutions were heated at 100° for 8 hr. In each case some insoluble material formed. The hydrolysates were neutralised with barium carbonate, clarified on the centrifuge, and assayed:

TABLE 4. *Plum-leaf photosynthesis experiments.*

Period of photosynthesis (hr.)	1	1·5	3	6	15·5	24	48
$^{14}CO_2$ supplied to leaves: Quantity (mmole)	8·83	9·05	8·83	8·98	8·94	8·77	9·17
$^{14}CO_2$ supplied to leaves: Specific activity (μc/mmole)	12·7	7·6	9·5	16·0	7·2	15·8	23·0
$^{14}CO_2$ supplied to leaves: Total activity (μc)	112	69	93	143	65	139	211
Activity found in: Leaf extracts (μc)	20·6	16·9	49·9	83·8	36·4	72·6	103·0
Activity found in: Insoluble leaf residue (μc)	7·0	6·6	23·2	57·2	26·4	53·8	68·2
Specific activity of carbon in leaf residue (μc/milli-atom-equiv.)	0·057	0·071	0·225	0·499	0·193	0·494	0·535
Wt. of insoluble leaf residue (g.)	3·35	2·50	2·82	3·12	3·72	2·97	3·40
% of carbon in leaf residue originating from $^{14}CO_2$ *	0·50	0·79	2·22	3·25	3·32	3·09	2·63

* Calc. on the basis of 3 g. of insoluble leaf residue.

the hydrolysates of the water-soluble, cold alkali-soluble, and hot alkali-soluble polysaccharide fractions contained approximately 3·3, 16, and 22 μc, respectively. The solutions were then evaporated and examination of the resultant syrups on the paper chromatogram indicated the presence of monosaccharides, traces of oligosaccharides, some ninhydrin-positive compounds, and some inorganic material. The monosaccharide constituents were: from the water-soluble polysaccharides, mainly galactose and arabinose (ratio *ca.* 1 : 1), with some galacturonic acid, rhamnose, xylose, and glucose, and a trace of 2-*O*-methylxylose; from the N-alkali-soluble polysaccharides, mainly glucose, smaller amounts of arabinose and xylose, and much smaller amounts of galactose, galacturonic acid, and rhamnose; and from the 2·5N-alkali-soluble polysaccharides, galactose, glucose, arabinose, and xylose (ratio *ca.* 1 : 2 : 2 : 1·5), smaller amounts of rhamnose and galacturonic acid, and traces of fucose and 2-*O*-methylxylose.[1] Autoradiographs of the paper chromatograms indicated that glucose was by far the most heavily labelled sugar, but activity was also detected in positions corresponding to galactose, arabinose, and rhamnose after the chromatograms had been left in contact with the emulsion side of *X*-ray films for 6 days.

The sugar mixtures were submitted to chromatography on paper sheets, with butan-1-ol–pyridine–water (10 : 3 : 3 v/v) as solvent. Particular attention was paid to obtaining each monosaccharide free from the others, and for galactose, glucose, and arabinose two separations were usually necessary. Galacturonic acid and small amounts of acidic oligosaccharides remained on the starting-line, and the former was purified by extracting the material from the starting-line with water and submitting it to paper chromatography (Whatman No. 540 paper) in ethyl acetate–acetic acid–water (9 : 2 : 2 v/v) solvent. The separated monosaccharides were eluted from the paper with cold water; the solutions of neutral sugars were then passed through columns of Amberlite IR-120(H) and IRA-400(CO_3) ion-exchange resins and evaporated to dryness. The galacturonic acid solution was passed through IR-120(H) resin only, and evaporated, the last few drops of water being removed *in vacuo* without heating. The sugar syrups were finally dried under reduced pressure over phosphoric oxide and weighed (see Table 5). Insufficient amounts of the minor constituents of the sugar mixtures were obtained for their further investigation. Ninhydrin-positive material could not be detected in any of the sugar syrups; the galactose and arabinose crystallised spontaneously, and the other neutral sugars did so when scratched. Galacturonic acid (10·3 mg.) from the water-soluble polysaccharide fraction contained some inorganic material (detected on the paper chromatogram); the optical rotation of the syrup $\{[\alpha]_D +49°$ (*c* 1·03)$\}$ indicated that it was *ca.* 90% pure.

Determination of Specific Activities of Isolated Monosaccharides.—The ^{14}C-labelled neutral monosaccharides were recrystallised from the appropriate solvents after sufficient amounts of the corresponding unlabelled sugars had been added to bring the weights to 30—60 mg. (in the case of glucose, *ca.* 200 mg.), and portions of the recrystallised sugars were then burnt and assayed. Crystalline derivatives of the galactose, arabinose, and xylose were then prepared

as follows, and their activities estimated by the same method. Galactose (25—30 mg.) was dissolved in 5N-nitric acid (3 c.c.) and the solution, contained in a 5 c.c. beaker, was heated on the steam-bath until the volume had decreased to *ca.* 0·5 c.c., and then the solution was set aside for 24 hr. to crystallise. The mucic acid so obtained (15—18 mg.) was washed with water, ethanol, and ether, and dried, and had m. p. 208—210°. To a solution of arabinose (25—30 mg.) in water (0·5 c.c.) was added benzhydrazide (35 mg.) in ethanol (0·5 c.c.). The solution was kept at 20° for 24 hr., then evaporated to dryness. Decolorisation (charcoal) and recrystallisation of the residue from methanol afforded arabinose benzoylhydrazone (20—25 mg.), m. p. 206—207°. Xylose (25—30 mg.) and toluene-*p*-sulphonhydrazide (40 mg.) were dissolved in methanol (4 c.c.) and the solution heated under reflux for ½ hr.[13] Then the solution was reduced in volume to *ca.* 1 c.c. and set aside (1—2 days) to crystallise. The xylose toluene-*p*-sulphonylhydrazone obtained (20—25 mg.) had m. p. 148—149°. The ^{14}C-labelled rhamnose (8 mg. remained after the first assay) yielded insufficient of the benzoylhydrazone for accurate ^{14}C determinations by the $Ba^{14}CO_3$ method. The ^{14}C-labelled galacturonic acid sample was dissolved in water and after the addition of sodium calcium D-galacturonate [$NaCa(C_6H_9O_7)_3.6H_2O$] (*ca.* 25 mg.) the solution was brought to pH 7 by addition of aqueous sodium and calcium hydroxides (molar ratio, 1 : 1). Crystalline ^{14}C-galacturonate (*ca.* 15 mg.) was then obtained by concentration and addition of ethanol.

The results of the assays were converted into the corresponding values for the undiluted radioactive monosaccharides and these are collected in Table 5.

TABLE 5.

		Sugar isolated (mg.)	Counts/min. per C atom of undiluted sugar calc. from assay results for: Diluted sugar	Sugar derivative	Specific activity of undiluted sugar (μc/milli-atom-equiv. of C)
Monosaccharides from water-soluble polysaccharides	D-Galactose	16·0	542	562	0·338
	L-Rhamnose	5·5	310	—	0·190
	L-Arabinose	14·0	521	525	0·320
	D-Xylose	2·6	[a]	70 [b]	0·043
	D-Galacturonic acid	9·3	27 [b]	—	0·017
Monosaccharides from polysaccharides soluble in cold N-NaOH	L-Arabinose	5·4	[a]	298	0·182
	D-Xylose	8·0	106 [b]	98 [b]	0·062
	D-Glucose	41·0	7170 [c]	—	4·40
Monosaccharides from polysaccharides soluble in hot 2·5N-NaOH	D-Galactose	19·7	587	562	0·350
	L-Rhamnose	8·1	374	—	0·227
	L-Arabinose	31·0	249	241	0·149
	D-Xylose	26·5	170	157	0·100
	D-Glucose	45·3	6130 [c]	—	3·76

[a] Diluted sugar not recrystallised and assayed, but used directly for preparation of derivative. [b] Probable error ±10%, calculated from variations in counting rate of $Ba^{14}CO_3$, which in these cases was not more than twice the background count. [c] Unchanged by recrystallisation; derivative not prepared.

We thank the Agricultural Research Council for the award of a Fellowship (to P. A.).

THE UNIVERSITY, BRISTOL. [*Received, July 8th,* 1958.]

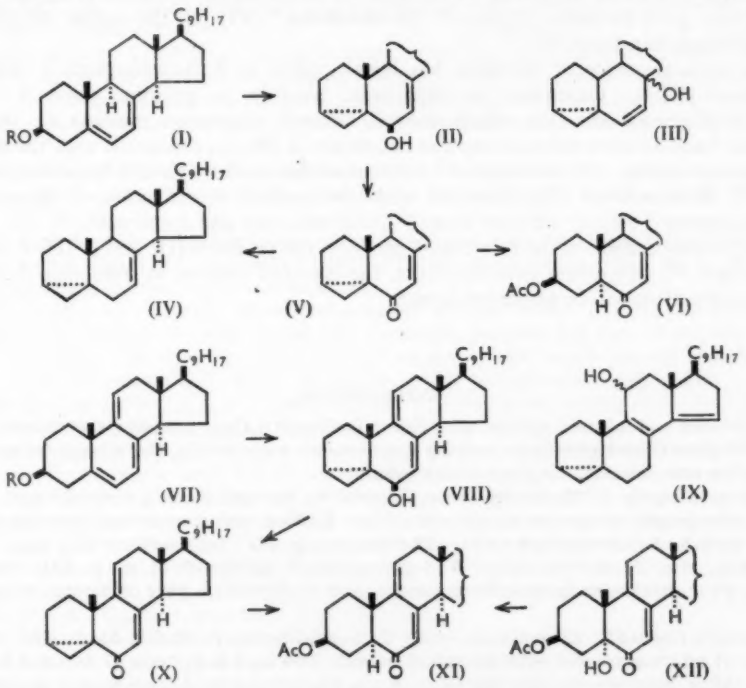
[13] Easterby, Hough, and Jones, *J.*, 1951, 3416.

905. 3 : 5-cyclo*Ergosta*-7 : 22-*dien*-6β-*ol* and 3 : 5-cyclo*Ergosta*-7 : 9(11) : 22-*trien*-6β-*ol*.

By G. H. R. Summers.

Chemical evidence confirming the correctness of the formulations of the compounds in the title given by Nes and Steele [1] is presented.

It is generally accepted that the formation of 6-substituted 3 : 5-*cyclo*-steroids by solvolysis of 3β-substituted Δ^5-steroids in buffered media involves the participation at position 3 of the π-electrons of the Δ^5-double bond. Nes and Steele [1] recently showed that in the 3 : 5-*cyclo*steroid rearrangement of 3β-substituted steroidal 5 : 7-dienes and 5 : 7 : 9(11)-trienes the same 1 : 3-interaction (homoallylic participation) occurs and that there is no



significant participation at position 3 by the 7 : 8- and the 9 : 11-double bond. Consequently, here also the main products are 6-substituted compounds and not the alternative products of anionotropic rearrangement. Thus ergosteryl toluene-*p*-sulphonate (I; R = $C_6H_4Me{\cdot}SO_2$) and dehydroergosteryl toluene-*p*-sulphonate (VII; R = $C_6H_4Me{\cdot}SO_2$) on hydrolysis in boiling aqueous acetone containing potassium acetate [2,3] or potassium hydrogen carbonate [1] yield 3 : 5-*cyclo*ergosta-7 : 22-dien-6β-ol (II) and 3 : 5-*cyclo*ergosta-7 : 9(11) : 22-trien-6β-ol (VIII) respectively, and not 3 : 5-*cyclo*ergosta-6 : 22-dien-8ξ-ol (III) and, for example, 3 : 5-*cyclo*ergosta-8(9) : 14 : 22-trien-11ξ-ol (IX), a possibility suggested by Nes and Shoppee.[3] We now describe some chemical and physical evidence which confirms the correctness of Nes and Steele's [1] formulations.

[1] Nes and Steele, *J. Org. Chem.*, 1957, **22**, 1457.
[2] Rees and Shoppee, *J.*, 1954, 3422; Nes, *J. Amer. Chem. Soc.*, 1956, **78**, 193.
[3] Nes and Shoppee, *J.*, 1957, 93.

3 : 5-*cyclo*Ergosta-7 : 22-dien-6β-ol (II) on oxidation with manganese dioxide in chloroform at 55° or chromium trioxide in pyridine at room temperature gave 3 : 5-*cyclo*ergosta-7 : 22-dien-6-one (V). The characteristic behaviour of allylic alcohols to the former reagent [4] and the demonstrated stability of the *cyclo*propane ring of 3 : 5-*cyclo*stanols to the latter reagent,[5] together with the ultraviolet absorption maximum at 249 mμ and the infrared carbonyl absorption maximum at 1642 cm.$^{-1}$, are in agreement with this structure. Chromium trioxide in pyridine also oxidises allylic alcohols to αβ-unsaturated ketones,[6] *e.g.*, 3β-acetoxyergosta-7 : 22-diene-5 : 6β-diol (cerevisteryl monoacetate) is smoothly converted into 3β-acetoxy-5α-hydroxyergosta-7 : 22-dien-6-one also prepared by oxidation with manganese dioxide.[7] Wolff–Kishner reduction of the ketone (V) yielded 3 : 5-*cyclo*ergosta-7 : 22-diene (IV) identical with the product obtained by Karrer and Asmis [8] by reduction of the diene ester (I; R = $C_6H_4Me{\cdot}SO_2$) with lithium aluminium hydride. Acid-catalysed hydration of the ketone (V) in acetic acid containing sulphuric acid, followed by acetylation, gave 3β-acetoxyergosta-7 : 22-dien-6-one [9] (VI) (cf. the similar treatment of 3 : 5-*cyclo*cholestan-6-one [10]).

The same sequence of reactions has been applied to 3 : 5-*cyclo*ergosta-7 : 9(11) : 22-trien-6β-ol (VIII). Oxidation by chromium trioxide in pyridine gave 3 : 5-*cyclo*-7 : 9(11) : 22-trien-6-one (X), which showed infrared absorption maxima at 1658 and 1616 cm.$^{-1}$ and an ultraviolet absorption maximum at 298 mμ consistent with the presence of a dienone system. Acid-catalysed hydration of this product yielded 3β-acetoxyergosta-7 : 9(11) : 22-trien-6-one (XI) identical with the product of reduction of 3β-acetoxy-5-hydroxyergosta-7 : 9(11) : 22-trien-6-one [11] (XII) with zinc and acetic acid.

The β-configuration of the 6-hydroxyl group in the products (II) and (VIII) is assumed by analogy; [12] supporting evidence from the infrared spectra of numerous 3 : 5-*cyclo*-steroid derivatives will be presented later.[6]

Experimental

Ultraviolet and infrared spectra were determined with a Cary recording spectrometer and a Grubb-Parsons GS2 double-beam grating spectrometer respectively, the solvent being alcohol and carbon tetrachloride. $[\alpha]_D$ are in chloroform.

3 : 5-*cyclo*Ergosta-7 : 22-dien-6β-ol was prepared by Nes and Steele's method [1] and purified by chromatography on neutral aluminium oxide. Elution with pentane and pentane–benzene gave a little 3 : 5-*cyclo*ergosta-6 : 8(14) : 22-triene, m. p. 103°, $[\alpha]_D$ +95° (*c* 1·1), $\lambda_{max.}$ 262 mμ (log ε 4·4); use of ether furnished 3 : 5-*cyclo*ergosta-7 : 22-dien-6β-ol, m. p. 131—133°, $[\alpha]_D$ −12° (*c* 0·8), after crystallisation from acetone, and of chloroform gave ergosterol, m. p. 163—165°.

3 : 5-cyclo*Ergosta*-7 : 22-*dien*-6-*one*.—(*a*) 3 : 5-*cyclo*Ergosta-7 : 22-dien-6β-ol (700 mg.) in pyridine (7 ml.) was treated with chromium trioxide (700 mg.) in pyridine (7 ml.) and left overnight. After dilution with ether the solution was filtered and the filtrate washed several times with water, dried (Na_2SO_4), and evaporated. The crystalline product crystallised from ether, to give 3 : 5-cyclo*ergosta*-7 : 22-*dien*-6-*one* as plates, m. p. 168—169°, $[\alpha]_D$ +43° (*c* 1·25), $\lambda_{max.}$ 249 mμ (log ε 4·13), $\nu_{max.}$ 1642 cm.$^{-1}$ [Found (after drying at 50°/0·05 mm. for 12 hr.): C, 85·3; H, 10·6. $C_{28}H_{42}O$ requires C, 85·2; H, 10·7%].

(*b*) 3 : 5-*cyclo*Ergosta-7 : 22-dien-6β-ol (150 mg.) in chloroform (50 ml.) was shaken at 55° for 5 hr. with activated manganese dioxide (3·5 g.). Filtration of the solution through neutral

[4] Amendolla, Rosenkranz, and Sondheimer, *J.*, 1954, 1226.
[5] Burn, Ellis, Petrow, Stuart-Webb, and Williamson, *J.*, 1957, 4092.
[6] Summers, unpublished work.
[7] Blears and Shoppee, *Chem. and Ind.*, 1953, 947.
[8] Karrer and Asmis, *Helv. Chim. Acta*, 1952, **35**, 1926.
[9] Barton and Robinson, *J.*, 1954, 3045.
[10] Ladenburg, Chakravorty, and Wallis, *J. Amer. Chem. Soc.*, 1939, **61**, 3483.
[11] Zürcher, Heusser, Jeger, and Geistlich, *Helv. Chim. Acta*, 1954, **37**, 1562.
[12] Shoppee and Summers, *J.*, 1952, 3361; Evans and Summers, *J.*, 1957, 906.

XUM

aluminium oxide followed by removal of the chloroform gave 3 : 5-*cyclo*ergosta-7 : 22-dien-6-one, m. p. and mixed m. p. 166—168° (from ether).

3β-*Acetoxy*-5α-*hydroxyergosta*-7 : 22-*dien*-6-*one*.—Cerevisteryl monoacetate (50 mg.) in pyridine (1 ml.) was treated with chromium trioxide (59 mg.) in pyridine (1 ml.) and the mixture left overnight. Working up in the usual way gave a solid (39 mg.) which on crystallisation from acetone gave 3β-acetoxy-5α-hydroxyergosta-7 : 22-dien-6-one, m. p. and mixed m. p. 268—269°, $[\alpha]_D$ −5° (*c* 0·4).

3β-*Acetoxyergosta*-7 : 22-*dien*-6-*one*.—3 : 5-*cyclo*Ergosta-7 : 22-dien-6-one (500 mg.) in acetic acid (100 ml.) was refluxed with 5N-sulphuric acid (25 ml.) for 2 hr., then poured into water, which was extracted with ether. The extract was washed with water and saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. The oily product was treated with acetic anhydride and pyridine overnight. The acetate (460 mg.) was chromatographed on aluminium oxide (15 g.). Elution with pentane–benzene (1 : 1) gave 3β-acetoxyergosta-7 : 22-dien-6-one (345 mg.) which from acetone formed needles, m. p. 185°, $[\alpha]_D$ −15° (*c* 1·1), $\nu_{max.}$ 1733 and 1675 cm.$^{-1}$, undepressed in m. p. on admixture with a specimen prepared by Barton and Robinson's method.[9]

3 : 5-cyclo*Ergosta*-7 : 22-*diene*.—Wolff–Kishner reduction of 3 : 5-*cyclo*ergosta-7 : 22-dien-6-one (250 mg.) in the usual way gave an oil (180 mg.) which on filtration in pentane through aluminium oxide and crystallisation from ether–methanol gave 3 : 5-*cyclo*ergosta-7 : 22-diene, m. p. 102—104°, identical (infrared spectrum) with a specimen obtained by Karrer and Asmis's procedure.[8]

3 : 5-cyclo*Ergosta*-7 : 9(11) : 22-*trien*-6β-*ol*.—This [1] was purified by filtration in ether through neutral aluminium oxide and crystallised from acetone as needles, m. p. 126°, $[\alpha]_D$ +129°, $\lambda_{max.}$ 247 mμ (log ε 4·19).

With methyl iodide and silver oxide (reflux for 8 hr.) it gave an oil which crystallised only on being seeded with 3 : 5-*cyclo*ergosta-7 : 9(11) : 22-trien-6β-yl methyl ether,[2] m. p. 56°. The infrared spectra of the specimens were identical.

3 : 5-cyclo*Ergosta*-7 : 9(11) : 22-*trien*-6-*one*.—3 : 5-*cyclo*Ergosta-7 : 9(11) : 22-trien-6β-ol (310 mg.) in pyridine (3 ml.) was treated with chromium trioxide (310 mg.) in pyridine (3 ml.) and left overnight. Working up as described above gave a solid which from ethyl acetate and ether gave 3 : 5-cyclo*ergosta*-7 : 9(11) : 22-*trien*-6-*one*, m. p. 152—154°, $[\alpha]_D$ +212° (*c* 1·56), $\lambda_{max.}$ 298 mμ (log ε 4·10), $\nu_{max.}$ 1658 and 1616 cm.$^{-1}$ [Found (after drying at 50°/0·05 mm. for 12 hr.): C, 85·3; H, 10·45. $C_{28}H_{40}O$ requires C, 85·7; H, 10·3%].

3β-*Acetoxyergosta*-7 : 9(11) : 22-*trien*-6-*one*.—(*a*) A solution of 3 : 5-*cyclo*ergosta-7 : 9(11) : 22-trien-6-one (1 g.) in acetic acid (200 ml.) containing 5N-sulphuric acid (50 ml.) was refluxed for 2 hr. Working up in the usual way, followed by acetylation of the product with acetic anhydride in pyridine, gave a red oil which was chromatographed on aluminium oxide (30 g.). Elution with pentane–benzene (9 : 1) gave an oil which on crystallisation from methanol gave 3β-*acetoxyergosta*-7 : 9(11) : 22-*trien*-6-*one*, m. p. 142—148°, $[\alpha]_D$ −36° (*c* 1·75), $\lambda_{max.}$ 293·5 mμ (log ε 4·75), $\nu_{max.}$ 1238, 1667, and 1739 cm.$^{-1}$ [Found (after drying at 50°/0·05 mm. for 12 hr.): C, 79·35; H, 9·3. $C_{30}H_{44}O_3$ requires C, 79·6; H, 9·8%].

(*b*) 3β-Acetoxy-5-hydroxyergosta-7 : 9(11) : 22-trien-6-one,[11] m. p. 239—242° (250 mg.), in acetic acid (30 ml.) was refluxed for 1 hr. with portion-wise addition of zinc dust (2 g.). Chromatography of the product on aluminium oxide (8 g.) and elution with pentane–benzene (9 : 1) gave 3β-acetoxyergosta-7 : 9(11) : 22-trien-6-one, m. p. 144—146° identical with the above specimen.

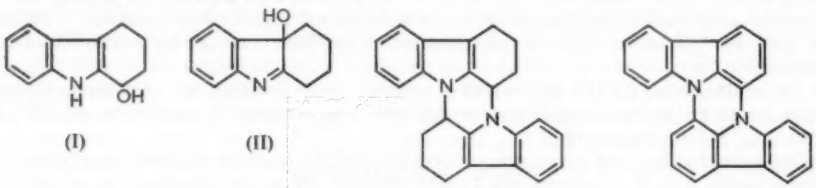
UNIVERSITY COLLEGE OF SWANSEA, UNIVERSITY OF WALES. [*Received, July 9th*, 1958.]

906. *The Synthesis of* 1 : 9-9′ : 1′-*Dicarbazolylene, and Related Experiments.*

By A. E. Jean Herbert and Muriel Tomlinson.

1 : 9-9′ : 1′-Dicarbazolylene has been synthesised by heating 1 : 6-diphenylphenazine *N*-oxide with palladium–charcoal. In a similar way 1-phenylphenazine 5-oxide afforded 5 : 10-dihydro-1 : 5-*o*-phenylenephenazine. Evidence is described which throws doubt on Wieland and Lecher's claim to have obtained 5 : 10-di-*p*-nitrophenylphenazine by heating 4-nitro-*N*-nitrosodiphenylamine.

The substance obtained by dehydration of 1 : 2 : 3 : 4-tetrahydro-1-hydroxycarbazole (I) and 1 : 2 : 3 : 4-tetrahydro-11-hydroxycarbazolenine (II), and first described as " 2 : 3-dihydrocarbazole," was later shown to have formula $C_{24}H_{22}N_2$ and not $C_{12}H_{11}N$. It seemed probable that it is really 1 : 2 : 3 : 4 : 1′ : 2′ : 3′ : 4′-octahydro-(1 : 9-9′ : 1′)-dicarbazolylene (III), and that the yellow substance obtained by its dehydrogenation is therefore 1 : 9-9′ : 1′-dicarbazolylene [1] (IV).



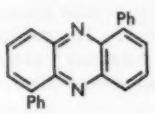
(I) (II) (III) (IV)

Several attempts to synthesise the compound (IV) have been described.[2] One was based on Wieland and Lecher's statement [3] that 4-nitro-*N*-nitrosodiphenylamine when boiled in xylene gives some 5 : 10-dihydro-5 : 10-di-*p*-nitrophenylphenazine. It was found [2] that 2-nitro-*N*-nitrosodiphenylamine did not afford 5 : 10-dihydro-5 : 10-di-*o*-nitrophenylphenazine, from which it had been hoped that 1 : 9 : 9′ : 1′-dicarbazolylene might be obtained by reduction, diazotisation, and internal coupling: the principal products of the decomposition are 2-nitrodiphenylamine and 2 : 4′-dinitrodiphenylamine, so it seemed possible that decomposition of *N*-nitrosodiphenylamines in which the *para*-positions are blocked, *e.g.*, by methyl groups or chlorine atoms, might better afford dihydrodi-*o*-nitrophenylphenazines of the type required. A number of such compounds were therefore prepared and investigated but the only products isolated (apart from the original 2-nitrodiphenylamine) were dinitrodiphenylamines. It was therefore, desirable to repeat Wieland and Lecher's work, and although we obtained a substance which roughly corresponded in properties and analysis to their " dihydrodi-*p*-nitrophenylphenazine " this was clearly not homogeneous. Chromatography of the product obtained as by them led to isolation of 4-nitrodiphenylamine, 4 : 4′-dinitrodiphenylamine, and 4 : 2′-dinitrodiphenylamine, and many small bands were seen on the alumina. When this work was nearing completion, Gilman and Dietrich [4] reported the synthesis of 5 : 10-dihydro-5 : 10-diphenylphenazine which was quite different from the substance which Wieland [5] had obtained by heating tetraphenylhydrazine in toluene. (Wieland attributed the formation of phenazine derivatives in both of the above reactions to the dimerisation of Ar_2N radicals formed by dissociation of nitrosamines and hydrazines.)

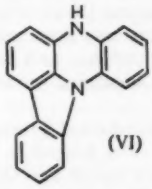
We employed many of the ways that have been described for preparing nitrodiphenylamines, but yields were generally poor and the method given seems the most satisfactory.

[1] Plant and Tomlinson, *J.*, 1931, **3324**; 1933, 298; 1950, 2127.
[2] Geale, Linnell, and Tomlinson, *J.*, 1956, 1124.
[3] Wieland and Lecher, *Annalen*, 1912, **392**, 165.
[4] Gilman and Dietrich, *J. Amer. Chem. Soc.*, 1957, **79**, 6178.
[5] Wieland, *Annalen*, 1911, **381**, 200.

We then hoped to prepare 1 : 9-9′ : 1′-dicarbazolylene by dehydrogenation of 1 : 6-diphenylphenazine (V) which we tried to prepare by Wohl and Aue's phenazine synthesis.[6] From 2-nitrodiphenyl and aniline we obtained 1-phenylphenazine, whereas from 2-aminodiphenyl and nitrobenzene the product was a phenazine oxide, presumably 1-phenylphenazine 5-oxide. This was reduced to 1-phenylphenazine. Our experiments showed that the use of benzene as solvent [7] greatly improves the Wohl and Aue phenazine synthesis, and in this way we obtained, from 2-nitrodiphenyl and 2-aminodiphenyl, 1 : 6-diphenylphenazine *N*-oxide, which was reduced to 1 : 6-diphenylphenazine with iron.



(V)



(VI)

When 1 : 6-diphenylphenazine *N*-oxide was heated with palladium–charcoal it was converted, in good yield, into 1 : 9-9′ : 1′-dicarbazolylene, identical in all respects with a specimen obtained from tetrahydrocarbazole in the original investigation. In a similar way 6 : 10-dihydro-1 : 6-*o*-phenylenephenazine (8*H*-indolo[3,2,1-*de*]phenazine) (VI was prepared from 1-phenylphenazine and from its *N*-oxide. Waterman and Vivian [8] claim to have prepared a substance with the structure (VI) (which they called 1 : 9-dihydrophenazininocarbazole) by heating 9-*o*-nitrophenylcarbazole with ferrous oxalate. They give neither m. p. nor analysis, and our attempts to repeat this reaction have been unsuccessful.

Experimental

4 : 4′-*Dimethyl*-2-*nitrodiphenylamine*.—A mixture of 4-chloro-3-nitrotoluene (24 g.), *p*-toluidine (42 g.), and anhydrous sodium acetate (24 g.) was heated at 190—200° (36 hr.), The product was washed with hydrochloric acid and steam-distilled from an acid solution. The remaining solid was collected, dried, and chromatographed on alumina (type H) in benzene. 4 : 4′-Dimethyl-2-nitrodiphenylamine was obtained as red plates, m. p. 85° (13 g.). Other diphenylamines were made similarly; *e.g.*, 4 : 4′-dichloro-2-nitrodiphenylamine (yield 48%), 4-chloro-4′-methyl-2-nitrodiphenylamine (97%), etc.

*4-Methyl-2′-nitro-*N*-nitrosodiphenylamine*. Potassium nitrite (2 g.), in a little water, was added to 4-methyl-2′-nitrodiphenylamine (4·6 g.) in glacial acetic acid (100 c.c.). After 1 hr. water was added. The precipitated *4-methyl-2′-nitro-*N*-nitrosodiphenylamine* recrystallised from alcohol as yellow plates, m. p. 102° (decomp.) (4·5 c.c.) (Found: C, 60·9; H, 4·4. $C_{13}H_{13}O_3N$ requires C, 60·7; H, 4·3%). In a similar way were obtained *4-chloro-2′-nitro-*, yellow prisms, m. p. 101° (from alcohol) (Found: Cl, 12·5. $C_{12}H_8O_3N_2Cl$ requires Cl, 12·8%), *4-chloro-4′-methyl-2-nitro-*, yellow plates, m. p. 96° (from alcohol) (Found: C, 53·3; H, 3·8. $C_{13}H_{10}O_3N_2Cl$ requires C, 53·6; H, 3·4%), and *4 : 4′-dimethyl-2-nitro-*N*-nitrosodiphenylamines*, yellow needles, m. p. 93° (from alcohol) (Found: C, 62·5; H, 4·9. $C_{14}H_{13}O_3N_2$ requires C, 62·0; H, 4·8%).

Decomposition of **4-*Methyl*-2′-*nitro*-N-*nitrosodiphenylamine*.**—This nitrosamine (5 g.) was heated in boiling xylene (5 c.c.) until evolution of nitric oxide ceased (1½ hr.). The xylene was distilled and the residue, in benzene, was chromatographed on alumina. Three fractions afforded, severally, 4-methyl-2′-nitrodiphenylamine, m. p. 68°, 4-methyl-2′ : 4′-dinitrodiphenylamine, m. p. 135° (Found: C, 57·0; H, 4·4. Calc. for $C_{13}H_{11}O_4N_3$: C, 57·1; H, 4·0%), and an unidentified 4-methyldinitrodiphenylamine, orange needles, m. p. 177° (Found: C, 57·3; H, 4·1%).

In a similar way 4 : 4′-dimethyl-2-nitro-*N*-nitrosodiphenylamine gave 4 : 4′-dimethyl-2-nitrodiphenylamine, m. p. 85°, and 4 : 4′-dimethyl-2 : 2′-dinitrodiphenylamine, orange plates, m. p. 199° (Found: C, 58·7; H, 4·7; N, 14·2. Calc. for $C_{14}H_{12}O_4N_2$: C, 58·5; H, 4·5; N, 14·6%),

[6] Wohl and Aue, *Ber.*, 1901, **34**, 2446.
[7] Pachter and Kloetzel, *J. Amer. Chem. Soc.*, 1951, **73**, 4958.
[8] Waterman and Vivian, U.S.P. 2,292,808.

and 4-chloro-2′-nitro-*N*-nitrosodiphenylamine gave 4-chloro-2′-nitrodiphenylamine, m. p. 143·5°, and 4-chloro-2′ : 4′-dinitrodiphenylamine, m. p. 165°.

Decomposition of 4-*Nitro*-N-*nitrosodiphenylamine*.—(*a*) Wieland and Lecher's experiment [3] was repeated, nitrosamine (5 g.) in xylene (25 c.c.) being used. The solvent was evaporated *in vacuo*, and the residue repeatedly extracted with alcohol. The insoluble fraction was dissolved in chloroform and precipitated with alcohol (3 times); the solid, m. p. 200—208° (sintering at 180°) (Found: C, 68·8; H, 4·9%), thus obtained did not appear to be crystalline. This, Wieland and Lecher claimed, was 5 : 10-dihydro-5 : 10-di-*p*-nitrophenylphenazine [they give m. p. 183°, not sharp, sintering at 154° (Found: C, 67·45; H, 4·1. $C_{24}H_{16}O_4N_4$ requires C, 67·9; H, 3·8%)]. (*b*) The nitrosamine (12 g.) was boiled in xylene (60 c.c.) until no more nitric oxide was evolved and the solvent was removed *in vacuo*. The product was extracted first with benzene and then with chloroform, and the two fractions were separately chromatographed on alumina. The products identified (mixed m. p.) were 4-nitro-, 4 : 2′-dinitro-, and 4 : 4′-dinitro-diphenylamine.

1-*Phenylphenazine*.—A mixture of 2-nitrodiphenyl [9] (5 g.), aniline (2·4 g.), and dry powdered potassium hydroxide (4 g.) was heated in boiling benzene (40 c.c.) for 24 hr., with stirring. The product was washed with water, and the dried benzene layer chromatographed on alumina. The first fraction contained 2-nitrodiphenyl, and the second gave a solid which crystallised from alcohol to give 1-*phenylphenazine* (0·54 g.) as yellow needles, m. p. 157° (Found: C, 84·3; H, 4·7. $C_{18}H_{12}N_2$ requires C, 84·4; H, 4·7%).

1-*Phenylphenazine* 5-*Oxide*.—This *oxide* was prepared in a similar way from 2-aminodiphenyl [10] (4·2 g.), nitrobenzene (3·13 g.), and potassium hydroxide (4 g.) in benzene (40 c.c.). It crystallised from alcohol as yellow needles, m. p. 198° (Found: C, 79·6; H, 4·6. $C_{18}H_{12}ON_2$ requires C, 79·4; H, 4·4%). When this oxide, in acetic acid, was shaken with zinc dust, and the green solution so obtained was (after filtration) exposed to air for 30 min. it became yellow. Addition of water to it then precipitated 1-phenylphenazine, m. p. 157°, identical with the above.

1 : 6-*Diphenylphenazine* N-*Oxide*.—This was prepared, as above, from 2-nitrodiphenyl (5 g.), 2-aminodiphenyl (4·2 g.), and potassium hydroxide (4 g.) in benzene (40 c.c.) (24 hr.). A solid separated and was collected. (The benzene layer contained only starting materials.) The solid was recrystallised from chloroform and afforded 1 : 6-*diphenylphenazine* N-*oxide* as yellow needles, m. p. 270° (1·1 g.) (Found: C, 83·0; H, 4·6; N, 7·9. $C_{24}H_{16}ON_2$ requires C, 82·7; H, 4·6; N, 8·0%).

1 : 6-*Diphenylphenazine*.—The last *N*-oxide (0·3 g.) was heated with iron powder in dry carbon dioxide at 300°. Crystals sublimed and recrystallisation from xylene gave 1 : 6-*diphenylphenazine* (0·2 g.) as yellow needles, m. p. 262—265° (Found: C, 86·7; H, 5·1. $C_{24}H_{16}N_2$ requires C, 86·7; H, 4·8%).

1 : 9-9′ : 1′-*Dicarbazolylene*.—When 1 : 6-diphenylphenazine *N*-oxide (0·35 g.) was mixed with 10% palladium–charcoal (0·5 g.) it became green: when heated in a stream of hydrogen (or carbon dioxide) fusion occurred at 270°, and at 400° the colour became yellow again; at 450° 1 : 9-9′ : 1′-dicarbazolylene began to sublime. Recrystallisation from xylene (the solution shows a vivid violet fluorescence) afforded the dicarbazolylene as yellow needles, m. p. 337° (0·3 g.), not depressed on admixture with a sample, m. p. 337°, prepared from tetrahydrocarbazole. The infrared spectra of the two samples were identical and the light absorption in dioxan, $\lambda_{max.}$ 2530, 2890, 3920, and 4140 Å (log ε 4·68, 4·35, 4·08, and 4·3), were also identical.

5 : 10-*Dihydro*-1 : 5-*o*-*phenylenephenazine* (8H-*indolo*[3,2,1-de]*phenazine* (VI).—1-Phenylphenazine 5-oxide (0·25 g.) was heated with palladium–charcoal (0·5 g.) as above. Fusion occurred at 200° and the green liquid became yellow at 330°. At 380° the product sublimed. Recrystallisation from benzene–light petroleum (b. p. 60—80°) afforded the pentacyclic *phenazine*, m. p. 190° (0·1 g.) (Found: C, 84·4; H, 4·7. $C_{18}H_{12}N_2$ requires C, 84·4; H, 4·7%). Solutions in benzene show intense blue-violet fluorescence; the infrared spectrum contains a sharp band at 3380 cm.$^{-1}$ (NH). $\lambda_{max.}$ in ethanol were at 2540, 2860, 3430, 3900 Å (log ε 4·75, 3·69, 3·51, and 3·67).

In a similar way 1-phenylphenazine (0·5 g.) also afforded this compound (0·2 g.).

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, July 17th*, 1958.]

[9] Elks, Haworth, and Hey, *J.*, 1940, 1285.
[10] Scarborough and Waters, *J.*, 1927, 91.

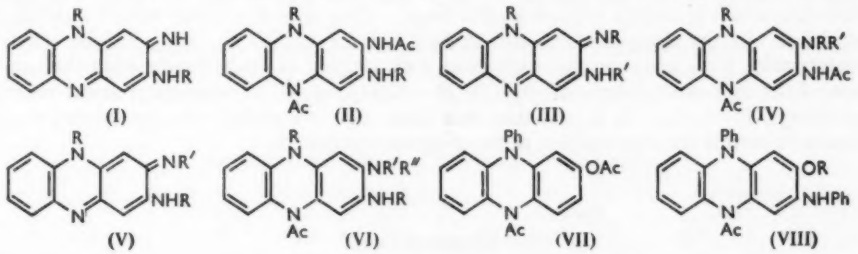
907. *The Oxidation of Derivatives of* o-*Phenylenediamine. Part VI.*[1] *Reductive Acylation of Anilinoaposafranines and Related Compounds.*

By VINCENT C. BARRY, J. G. BELTON, J. F. O'SULLIVAN, and DERMOT TWOMEY.

Anilino*apo*safranines and related compounds have a *p*-quinonoid system which is readily reduced. The products of catalytic hydrogenation have little colour but are rapidly reoxidised in air to their original state. Hydrogenation in the presence of acetic or propionic anhydride yields stable non-quinonoid compounds containing 1—3 acyl groups. The therapeutic effect of the " rimino "-compounds in mouse tuberculosis is completely lost on reductive diacylation, indicating that the *p*-quinonoid system is involved in the antimycobacterial activity. Two reduced monoacetylated rimino-derivatives retained activity *in vivo*: it is presumed that these compounds are deacetylated in the tissues, regenerating the original active compounds.

ANILINO*apo*SAFRANINE and the related phenazine derivatives described in previous papers of this series contain a *p*-quinonoid system which may be readily reduced, and the unstable reduced compounds are spontaneously re-oxidised in air. It has been suggested[2,3] that, among other factors, the antituberculosis activity of these compounds depends on the *p*-quinonoid system which enables them to become involved in the terminal stages of the respiratory metabolism of the bacillus. Further, the reduced compounds on re-oxidation liberate hydrogen peroxide which may also play a part in the antimicrobial activity. It was of interest therefore to stabilise the reduced non-quinonoid compounds with a view to ascertaining whether the altered molecules had lost the power to protect mice from the usual experimental tuberculosis infection.

Anilino*apo*safranine (I; R = Ph), on hydrogenation in acetic anhydride at room temperature and pressure in the presence of Adams catalyst, yields the diacetyldihydrophenazine (II; R = Ph). Its isomer (III; R = Ph, R′ = H) under similar conditions yields the diacetyl derivative (IV; R = Ph, R′ = H). The last compound, in boiling



ethanolic sodium hydroxide, readily loses an acetyl group to give the monoacetyl derivative (III; R = Ph, R′ = Ac), identical with the compound resulting from the reaction of hot acetic anhydride with the amino-derivative (III; R = Ph, R′ = H). The " rimino "-compound[1] (V; R = R′ = Ph) forms only a monoacetyl derivative (VI; R = R′ = Ph, R″ = H), indicating that the –NH– group of the arylamino-substituent is not acetylated under these conditions, and this has been confirmed with all the other compounds of this type investigated. On the other hand, when the hydrogen of the =NH group present in structure (I) is replaced by *iso*propyl, *cyclo*pentyl, or *cyclo*hexyl, reductive acetylation leads to the formation of a diacetyl derivative (VI; R = Ar, R′ = Ac, R″ = Pr^i, *cyclo*pentyl, or *cyclo*hexyl).

[1] Part V, Barry, Belton, O'Sullivan, and Twomey, *J.*, 1958, 859.
[2] Barry, Conalty, and Gaffney, *J. Pharm. Pharmacol.*, 1956, **8**, 1089.
[3] Barry, Belton, Conalty, Denneny, Edward, O'Sullivan, Twomey, and Winder, *Nature*, 1957, **179**, 1013.

XUM

The behaviour of compound (V; R = C_6H_4Cl-*p*, R′ = *cyclo*heptyl) however was exceptional: only one acetyl group entered the molecule, presumably on the reduced nitrogen at the 10-position to give compound (VI; R = C_6H_4Cl-*p*, R′ = *cyclo*heptyl, R″ = H). The failure to acetylate the N^3-position suggested that steric influences were responsible, and this was confirmed subsequently by the isolation of monoacetylated derivatives from compound (V; R = Ph) when R′ was *tert.*-butyl, and from compounds (V; R = C_6H_4Cl-*p*) when R′ was 2-methyl*cyclo*hexyl and *cyclo*octyl.

The monoacetyl derivative (VI; R = C_6H_4Cl-*p*, R′ = *cyclo*heptyl, R″ = H) may also be prepared by catalytic hydrogenation of the corresponding glyoxalinophenazine [1] in acetic anhydride, the glyoxalino-ring being opened at the same time. As expected the amino-compound (III; R = *cyclo*hexyl, R′ = H) yields a triacetyl derivative (IV; R = *cyclo*hexyl, R′ = Ac).

Hydrogenated *apo*safranone derivatives are also stabilised by acetylation. Thus, *apo*safranone gives the diacetylated compound (VII) whereas anilino*apo*safranone gives the monoacetyl derivative (VIII; R = H), acetylation of the phenolic hydroxyl being hindered probably by hydrogen-bonding with the 2-anilino-group. Further treatment of the hydroxy-compound (VIII; R = H) by warm acetic anhydride brings about acylation of the phenolic hydroxyl group, to give the diacetyl derivative (VIII; R = Ac). When propionic anhydride was used in the reductive acylation of the compounds (V; R = C_6H_4Cl-*p*, R′ = *cyclo*hexyl and *cyclo*heptyl) the results obtained were similar to those with acetic anhydride.

In most cases mild treatment with alkali of the reduced acetylated compounds regenerates the original quinonoid pigments. However, the diacetyl derivative (II; R = Ph) and the triacetyl derivative (IV; R = *cyclo*hexyl, R′ = Ac) are extensively decomposed by alkali; the acetoxy-compound (VII) regenerates *apo*safranone on treatment with sodium nitrite, and the phenol (VIII; R = H) is reconverted into anilino*apo*safranone on exposure to ultraviolet radiation. As already stated, compound (IV; R = Ph, R′ =H) may be hydrolysed by ethanolic alkali in two stages.

All the acylated reduced compounds are colourless, crystalline, and reasonably stable materials which gradually acquire a pink tinge. They appear to some extent to be light-sensitive. Of the compounds tested all had lost the ability on oral administration to protect mice from an intravenous infection with virulent tubercle bacilli, with the exception of the monoacetyl derivatives (VI; R = C_6H_4Cl-*p*, R′ = *cyclo*heptyl and 2-methyl-*cyclo*hexyl, R″ = H). It is probable that these two compounds are hydrolysed in the tissues to permit the regeneration of the *p*-quinonoid system.

Experimental

Light petroleum had b. p. 40—60°, ligroin had b. p. 100—120°.

5-Acetyl-2 : 3-dianilino-5 : 10-dihydro-10-cyclohexylphenazine.—2-Anilino-3 : 5-dihydro-5-*cyclo*hexyl-3-phenyliminophenazine (0·9 g.), acetic anhydride (90 c.c.), and Adams catalyst (0·1 g.) were shaken in hydrogen for 3 hr. The mixture was poured into ice-water (1 l.), and the precipitate collected, washed with water, and dried in a vacuum-desiccator. The *monoacetyl derivative* crystallised from benzene–light petroleum as off-white needles (0·7 g.), m. p. 202—203° (Found: C, 79·7; H, 6·6; N, 10·6. $C_{32}H_{32}ON_4,\frac{1}{2}C_6H_6$ requires C, 79·7; H, 6·6; N, 10·6%).

2-Acetoxy-5-acetyl-5 : 10-dihydro-10-phenylphenazine (VII).—Reductive acetylation of *apo*safranone gave the *diacetyl compound* (VII) as off-white needles, m. p. 172—173° (Found: C, 74·1; H, 5·2; N, 7·7. $C_{22}H_{18}O_3N_2$ requires C, 73·7; H, 5·0; N, 7·8%).

5-Acetyl-3-anilino-5 : 10-dihydro-2-hydroxy-10-phenylphenazine (VIII; R = H).—Reductive acetylation of anilino*apo*safranone yielded the monoacetyl derivative in almost colourless fluffy needles, m. p. 210—212° (from chloroform–light petroleum) (Found: C, 76·0; H, 5·2; N, 10·3. $C_{26}H_{21}O_2N_3$ requires C, 76·7; H, 5·2; N, 10·3%).

XUM

2-Acetoxy-5-acetyl-3-anilino-5 : 10-dihydro-10-phenylphenazine (VIII; R = Ac).—The preceding compound, when heated with acetic anhydride on the water-bath for 20 min., gave the *diacetyl derivative*, m. p. 158—160° (from benzene–light petroleum) (Found: C, 75·1 H, 5·4; N, 9·5. $C_{28}H_{22}O_3N_2$ requires C, 74·8; H, 5·1; N, 9·4%).

2-p-*Chloroanilino*-5-p-*chlorophenyl*-5 : 10-*dihydro*-3-(N-cyclo*hexylpropionamido*)-10-*propionylphenazine*.—2-*p*-Chloroanilino-5-*p*-chlorophenyl-3 : 5-dihydro-3-*cyclo*hexyliminophenazine (1·5 g.), propionic anhydride (150 c.c.), and Adams catalyst (0·1 g.) were shaken in hydrogen for 3 hr. and poured into ice-water. The fine precipitate was washed with water and dried. The *dipropionyl compound* (0·8 g.), crystallised from benzene–light petroleum, had m. p. 235—236° (Found: C, 70·7; H, 5·8; N, 8·4; Cl, 10·6. $C_{36}H_{36}O_2N_4Cl_2,\frac{1}{2}C_6H_6$ requires C, 70·3; H, 5·85; N, 8·4; Cl, 10·65%).

2-p-*Chloroanilino*-5-p-*chlorophenyl*-5 : 10-*dihydro*-3-cyclo*heptylamino*-10-*propionylphenazine*.—2-*p*-Chloroanilino-5-*p*-chlorophenyl-3 : 5-dihydro-3-*cyclo*heptyliminophenazine was reductively propionylated and gave the *monopropionyl derivative* (almost white needles), m. p. 220—221° (Found: C, 70·9; H, 6·0; N, 8·9; Cl, 11·4. $C_{34}H_{34}ON_4Cl_2,\frac{1}{2}C_6H_6$ requires C, 70·7; H, 5·9; N, 9·2; Cl, 11·6%).

2″-*Methyl*-5 : 1′-*di*-(p-*chlorophenyl*)*glyoxalino*(5′ : 4′-2 : 3)*phenazine*-2′-spiro-1″-cyclo*hexane*.—2-Amino-4′-chlorodiphenylamine hydrochloride (5 g.), 2-methyl*cyclo*hexanone (3 c.c.), and ethanol (100 c.c.) were treated with *p*-benzoquinone (5 g.) in aqueous ethanol (2 : 1; 180 c.c.) at 30°. After 1 hr. the solution was made alkaline and diluted with water. The precipitate was dried and chromatographed in benzene on alumina. The *glyoxalinophenazine* was obtained as orange-yellow crystals (2·8 g.), m. p. 263—265°, from benzene (Found: C, 71·0; H, 5·0; N, 10·7; Cl, 13·6. $C_{31}H_{26}N_4Cl_2$ requires C, 70·9; H, 4·95; N, 10·7; Cl, 13·5%).

2-p-*Chloroanilino*-5-p-*chlorophenyl*-3 : 5-*dihydro*-3-(2-*methyl*cyclo*hexylimino*)*phenazine*.—Catalytic hydrogenation [1] of the above glyoxalino-compound yielded the "*rimino*"-*compound* as red needles, m. p. 203—204° (from ethanol) (Found: C, 70·5; H, 5·25; N, 10·7; Cl, 13·5. $C_{31}H_{28}N_4Cl_2$ requires C, 70·6; H, 5·3; N, 10·6; Cl, 13·5%).

5 : 1′-*Di*-(p-*chlorophenyl*)*glyoxalino*(5′ : 4′-2 : 3)*phenazine*-2′-spirocyclo-1″-*octane*.—2-Amino-4′-chlorodiphenylamine hydrochloride (7 g.), *cyclo*octanone (3 g.), and ethanol (120 c.c.) were treated with *p*-benzoquinone (7 g.) in aqueous ethanol (2 : 1; 200 c.c.) at 30°. The *compound* was purified as before, yielding orange crystals (0·8 g.), m. p. 265—266°, from benzene–ligroin (Found: C, 71·4; H, 5·3; N, 10·3; Cl, 13·4. $C_{32}H_{28}N_4Cl_2$ requires C, 71·2; H, 5·2; N, 10·4; Cl, 13·2%).

2-p-*Chloroanilino*-5-p-*chlorophenyl*-3 : 5-*dihydro*-3-cyclo*octyliminophenazine*.—Catalytic hydrogenation of the above glyoxalinophenazine yielded dark-red needles, m. p. 221—222° (Found: C, 71·1; H, 5·35; N, 10·45; Cl, 13·0. $C_{32}H_{30}N_4Cl_2$ requires C, 71·0; H, 5·5; N, 10·35; Cl, 13·1%).

Acetylated derivatives of 5 : 10-*dihydrophenazine*.

			Found (%)					Required (%)			
		M. p.	C	H	N	Cl	Formula	C	H	N	Cl
(II) R = Ph		255° *	74·8	5·4	11·9	—	$C_{28}H_{24}O_2N_4$	75·0	5·4	12·5	—
Compounds (IV)											
R = *cyclo*Hexyl; R′ = Ac		273—274	71·6	7·4	11·1	—	$C_{30}H_{32}O_3N_4$	71·7	7·6	11·1	—
R = Ph; R′ = H		120 *	75·8	5·6	11·7	—	$C_{28}H_{24}O_2N_4,\frac{1}{2}C_6H_6$	75·9	5·5	11·8	—
Compounds (VI; R = Ph)											
R′	R″										
Bu^t	H	226—227	78·5	6·2	11·3	—	$C_{30}H_{30}ON_4,\frac{1}{2}C_6H_6$	78·7	6·6	11·5	—
*cyclo*Hexyl	Ac	209—210	77·6	6·5	9·7	—	$C_{34}H_{34}O_2N_4,\frac{1}{2}C_6H_6$	77·7	6·5	10·1	—
Ph	H	300	79·0	5·5	11·1	—	$C_{32}H_{26}ON_4$	79·7	5·4	11·6	—
Compounds (VI; R = C_6H_4Cl-*p*)											
R′	R″										
Pr^i	Ac	201—202	69·3	5·6	9·1	11·1	$C_{31}H_{28}O_2N_4Cl_2$	69·7	5·3	8·6	11·1
*cyclo*Pentyl	Ac	115—116	69·0	5·3	9·0	11·3	$C_{33}H_{30}O_2N_4Cl_2,\frac{1}{2}C_6H_6$	69·2	5·3	9·0	11·3
2-Me-*cyclo*hexyl	H	190 *	69·6	5·9	9·6	12·4	$C_{32}H_{32}ON_4Cl_2$	69·4	5·6	9·8	12·4
*cyclo*Heptyl	H	187—189	70·7	5·7	9·3	11·7	$C_{33}H_{36}ON_4Cl_2$	70·6	5·4	9·4	11·9
*cyclo*Octyl	H	171—172	70·9	6·0	8·7	11·1	$C_{34}H_{34}ON_4Cl_2,\frac{1}{2}C_6H_6$	71·2	5·9	9·0	11·4

* Decomp.

The data for the remaining *compounds* are tabulated. Acetyl determinations were unsatisfactory and not reproducible.

The biological results will be published elsewhere.

Grateful acknowledgment is made to J. R. Geigy S.A., Basle, Switzerland, for financial aid.

LABORATORIES OF THE MEDICAL RESEARCH COUNCIL OF IRELAND,
TRINITY COLLEGE, DUBLIN. [*Received, July 23rd*, 1958.]

---

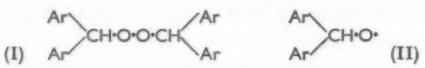
908. *Organic Peroxides. Part II.* The Decomposition of Bisdiphenylmethyl Peroxide.*

By J. I. G. CADOGAN, D. H. HEY, and W. A. SANDERSON.

Bisdiphenylmethyl peroxide has been prepared and its thermal decomposition in organic solvents studied. The reactions in bromobenzene, *iso*propylbenzene, and nitrobenzene are homolytic and give mainly benzophenone. In nitrobenzene at 210°, but not at 115°, phenyl radicals (0·03 mole/mole of peroxide) are also formed. The peroxide decomposes in ethanolic sodium ethoxide and in pyridine to give benzophenone and diphenylmethanol, probably by heterolysis.

SECONDARY aliphatic peroxides, where the substituent groups are aromatic, have received little attention. Davies *et al.*,[1] in an attempt to prepare di-*p*-methoxyphenylmethyl hydroperoxide, produced bis(di-*p*-methoxyphenylmethyl) peroxide (I; Ar = *p*-MeO·C_6H_4), but their method was not of general application. Earlier, Nauta [2] and his co-workers claimed to have isolated bis(di-2 : 4-dimethylphenylmethyl) peroxide and its 3 : 5-isomer from the reaction of the corresponding diphenylmethyl chloride with silver in the presence of oxygen. The yields were low, however, and the products were impure.

The preparation and decomposition of the hitherto unknown bisdiphenylmethyl peroxide (I; Ar = Ph) are now described. Attempts to prepare it by the condensation of diphenylmethyl hydroperoxide with diphenylmethanol (benzhydrol) in the presence of



toluene-*p*-sulphonic acid, by the method described by Hey, Stirling, and Williams [3] for the preparation of tertiary peroxides, gave low yields of the peroxide contaminated by much bisdiphenylmethyl ether. The similarity in the melting points of the peroxide and the ether (112—113° and 110—111° respectively) and in their solubilities precluded a satisfactory separation, although small quantities of bisdiphenylmethyl peroxide were isolated after tedious fractional crystallisation. Further, it was found that appreciable amounts of bisdiphenylmethyl ether could be present in a sample of the peroxide without producing a large change in melting point. This, coupled with the incomplete reaction of the peroxide with acid potassium iodide, made it difficult to assess the purity of the product. This difficulty was overcome by the use of an infrared spectrographic method of analysis based on a strong absorption band (9·5 μ) in the spectrum of bisdiphenylmethyl ether which was absent from that of the peroxide. By this means it was found that the condensation of diphenylmethanol with diphenylmethyl hydroperoxide, when carried out in acetic acid, gave almost pure bisdiphenylmethyl peroxide.

* Part I, *J.*, 1957, 1054.

[1] Davies, Foster, and White, *J.*, 1954, 2200.
[2] Nauta, Ernsting, and Faber, *Rec. Trav. chim.*, 1941, **60**, 915; Nauta and Wuis, *ibid.*, 1938, **57**, 41.
[3] Hey, Stirling, and Williams, *J.*, 1957, 1054.

XUM

By analogy with the decomposition of related peroxides [4] it would be expected that bisdiphenylmethyl peroxide would give the radical (II; Ar = Ph) on thermal decomposition in solution. In theory, this radical can break down in two ways: (*a*) by elimination of a hydrogen atom with the formation of benzophenone, or (*b*) by the elimination of a phenyl radical with the formation of benzaldehyde. Our experiments were designed to distinguish between these possibilities.

Bisdiphenylmethyl peroxide was allowed to decompose in bromobenzene, *iso*propylbenzene, and nitrobenzene at various temperatures. The results are summarised in Table 1, in which the figures, unless otherwise stated, refer to moles/mole of peroxide.

TABLE 1.

Solvent	$PhNO_2$		PhPr			PhBr–*p*-benzoquinone
Expt. No.	1 *	2	3 †	4 ‡	5 ‡	6 §
Peroxide (mmoles)	27·3	8·2	6·8	6·8	6·8	16·6
Temp.	210°	115°	152°	115°	115°	157°
Time (days)	(24 hr.)	7	7	7	7	137 (hr.)
Vol. of solvent (ml.)	400	120	100	100	100	200
Ph_2CO	1·48	1·69	1·40	1·57	1·60	1·40
$Ph_2CH{\cdot}OH$	0·03	0·08	0·48	0·30	0·28	—
Di-α-cumyl	—	—	0·18	0·12	0·12	—
Peroxide accounted for (%)	75	88	97	94	94	70

* Nitrodiphenyls (0·03 mole/mole) were formed.
† $Ph_2CH{\cdot}O{\cdot}CHPh_2$ (0·026 mole/mole) was formed.
‡ Reactions carried out under N_2 in the dark.
§ Quinhydrone (0·58 mole/mole) was formed.

It is considered that decompositions in these solvents proceed by the initial production of a diphenylmethoxy-radical (II; Ar = Ph) which either loses a hydrogen atom to give benzophenone, or reacts by combination with another hydrogen atom, either free or bound, as in *iso*propylbenzene, to give diphenylmethanol:

$$Ph_2CH{\cdot}O{\cdot} \longrightarrow Ph_2CO + H{\cdot}$$
$$Ph_2CH{\cdot}O{\cdot} \xrightarrow[\text{acceptor}]{\text{hydrogen}} Ph_2CO \qquad \text{(i)}$$

$$Ph_2CH{\cdot}O{\cdot} + H{\cdot} \longrightarrow Ph_2CH{\cdot}OH \qquad \text{(ii)}$$

$$Ph_2CH{\cdot}O{\cdot} + PhCH(CH_3)_2 \longrightarrow Ph_2CH{\cdot}OH + Ph\dot{C}(CH_3)_2 \qquad \text{(iii)}$$

$$2Ph\dot{C}(CH_3)_2 \longrightarrow Ph{\cdot}C(CH_3)_2{\cdot}C(CH_3)_2Ph \qquad \text{(iv)}$$

The formation of di-α-cumyl (iv) is taken as proof that free radicals are involved in the reaction. It is significant that the amount of di-α-cumyl (2 : 3-dimethyl-2 : 3-diphenylbutane) produced does not exceed the amount of diphenylmethanol formed. It seems unlikely, therefore, that hydrogen atoms abstract hydrogen from cumene, to give cumyl radicals, in this reaction. The formation of a small amount of aniline in the experiment with nitrobenzene, and the formation of quinhydrone in the reaction in bromobenzene in the presence of *p*-benzoquinone, affords strong support for reactions (i). These results do not, however, enable us to decide whether hydrogen atoms are involved, or whether benzophenone is produced by bimolecular reaction of the radical $Ph_2CHO{\cdot}$ with a hydrogen acceptor (nitrobenzene or *p*-benzoquinone [5]). On the other hand, the formation of benzophenone in the reaction in cumene can hardly be explained on the basis of a bimolecular reaction, because cumene would be expected to donate, as in reaction (iii), rather than to accept a hydrogen atom. The other possible hydrogen acceptor present is the diphenylmethoxy-radical itself:

$$2Ph_2CHO{\cdot} \longrightarrow Ph_2CO + Ph_2CH{\cdot}OH$$

[4] Hawkins, *Quart. Rev.*, 1950, **4**, 251.
[5] Horeld and Huisgen, *Annalen*, 1949, **562**, 137.

but this formulation is inconsistent with the stoicheiometry of the reaction, since, in all cases, the amount of benzophenone isolated is far in excess of the amount of diphenylmethanol formed. Indeed, appreciable amounts of diphenylmethanol were formed only in the experiments with cumene, and can be readily explained by invoking reaction (iii).

Only in one instance, that of the decomposition in nitrobenzene at the higher temperature (210°), was any evidence found for the formation of phenyl radicals. Chromatography of the products gave a fraction which was shown by infrared spectrography to consist of benzophenone with a mixture of nitrodiphenyls, of the same composition as that produced in the free-radical phenylation of nitrobenzene. This is the first recorded instance of the formation of a phenyl radical from the decomposition of an aliphatic peroxide.

The reluctance with which a phenyl radical is produced from the radical (II; Ar = Ph) is in agreement with observations on the decomposition of related peroxides and with Kharasch, Fono, and Nudenberg's [6] statement that the relative tendency of groups R, R', or R'' in the radical RR'R''C·O· to participate in cleavage of the R–C bond increases in the order Ph, Me, Et, H.

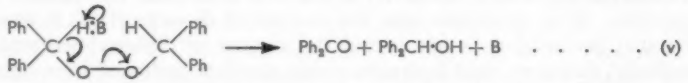
Bisdiphenylmethyl peroxide was also allowed to decompose in pyridine at 115°. In contrast to the above reactions, inconsistent results were repeatedly obtained, as indicated in Table 2.

TABLE 2. *Decomposition of bisdiphenylmethyl peroxide in pyridine at* 115°.

Expt. No.	Time (days)	Ph_2CO (moles/mole of peroxide)	$Ph_2CH{\cdot}OH$ (moles/mole of peroxide)	$(Ph_2CH)_2O$ (moles/mole of peroxide)	$\frac{Ph_2CO}{Ph_2CH{\cdot}OH}$	$\frac{Ph_2CO}{Ph_2CH{\cdot}OH}$ Corr.*	Recovery (%)
7	3·5	0·95	0·89	0	1·07	1·07	92
8	4	1·51	0·42	0	3·6	3·6	97
9	7	0·97	0·92	0	1·05	1·05	95
10	7	1·03	0·58	0·104	1·78	1·30	91
11	10	0·99	0·80	0·083	1·24	1·02	97
12 †	3	0·97	0·80	0·065	1·21	1·04	95
13 †	3	0·98	0·94	0	1·04	1·04	96

* *I.e.*, by assuming $(Ph_2CH)_2O$ to be derived from $Ph_2CH{\cdot}OH$.
† Reactions carried out under nitrogen in the dark.

It is believed that the main reaction is a base-catalysed decomposition of the peroxide producing equivalent amounts of benzophenone and diphenylmethanol, as observed in experiments 7, 9, and 13. The results of experiment 8 could be rationalised by assuming an initial reaction as in (v) followed by conversion of some diphenylmethanol into benzophenone, while the formation of bisdiphenylmethyl ether (expts. 10, 11, and 12) could be



. . . . . (v)

explained by self-condensation of diphenylmethanol. A supplementary experiment involving pyridine and diphenylmethanol, in which very small amounts of the ether and benzophenone were formed, indicated however that these explanations are unsatisfactory. Although rigorously purified materials were used in the experiments it is difficult to explain the inconsistencies beyond invoking catalysis by traces of impurities. That the reaction in pyridine is heterolytic is supported by the results of a similar experiment in 2 : 6-lutidine. The products were benzophenone and diphenylmethanol, and no trace of any compound resulting from free-radical attack on the side chains was isolated or detected.

The decomposition of the peroxide in ethanolic sodium ethoxide gave benzophenone (0·27 mole/mole) and diphenylmethanol (1·58 moles/mole). A control experiment showed that under these conditions benzophenone is converted into diphenylmethanol in sufficient quantity to suggest that the initial reaction of the peroxide with sodium ethoxide is also

[6] Kharasch, Fono, and Nudenberg, *J. Org. Chem.*, 1950, **15**, 763.

of type (v), producing equivalent amounts of benzophenone and diphenylmethanol. The above reduction of benzophenone closely parallels the well-known reaction in propan-2-ol, when benzpinacol (1 : 2-diphenylethanediol) is first produced and then reduced to diphenylmethanol.[7]

Chromatography on alumina of a benzene solution of the peroxide gave an equimolar mixture of benzophenone and diphenylmethanol, thus providing a third example of base-catalysed decomposition.

Experimental

Chromatographic separations were carried out on activated alumina (Peter Spence & Sons, Ltd., Type " H ").

Solvents.—Nitrobenzene (" AnalaR ") was washed with aqueous sodium hydroxide (25%) until the washings were colourless, steam distilled, dried ($CaCl_2$), fractionally distilled through a 120 cm. helix-packed column, and finally fractionally frozen (3 times). Pyridine (" AnalaR ") was dried (KOH) and fractionally distilled (120 cm. column) from barium monoxide. *iso*Propylbenzene was washed with sulphuric acid (*d* 1·8) until the washings were colourless, then with aqueous sodium hydrogen carbonate. After being dried ($CaCl_2$), the solvent was fractionally distilled (120 cm. column). The product was passed through an alumina column to remove hydroperoxide immediately before use. Bromobenzene was washed with aqueous sodium hydroxide (7N; 3 times), dried (Na_2SO_4), and fractionally distilled (120 cm. column). Bisdiphenylmethyl ether,[8] recrystallised from chloroform–ethanol, had m. p. 110—111°.

Diphenylmethyl hydroperoxide was prepared by a modification of the method of Davies, Foster, and White.[9] To hydrogen peroxide (86% w/w; 25 ml.; 6·3 mol.), sulphuric acid (*d* 1·8; 0·10 ml.), and ether (20 ml.), was added diphenylmethanol (30 g.; 0·16 mol.; m. p. 66°, Hopkin and Williams reagent crystallised from light petroleum, b. p. 60—80°) in ether (15 ml.). The mixture was stirred magnetically for 6 hr. at room temperature. The usual precautions against explosion were taken. Water (50 ml.) was added, the mixture was separated, and the aqueous layer was extracted with ether (3 × 20 ml.). The ether solution was washed with sodium hydrogen carbonate solution and with water, and was dried (Na_2SO_4). Evaporation of the solution left the crude hydroperoxide (30 g.; 92%; m. p. 40—45°). Recrystallisation from light petroleum (b. p. 60—80°) gave diphenylmethyl hydroperoxide as colourless needles, m. p. 48—50°. Davies *et al.*[9] report m. p. 50—52°.

Bisdiphenylmethyl Peroxide.—Attempts to prepare the peroxide, based on the general method described by the Hercules Powder Co.,[10] from diphenylmethanol (excess of 1 mol.) and diphenylmethyl hydroperoxide (1 mol.) in the presence of toluene-*p*-sulphonic acid (catalytic quantity) under various conditions of time and temperature, gave mixtures of bisdiphenylmethyl ether and bisdiphenylmethyl peroxide which could not be satisfactorily resolved. Traces of the ether mixed with the peroxide were detected by infrared spectrography as described above. The following method of preparation was found to be satisfactory: Diphenylmethanol (5 g.), diphenylmethyl hydroperoxide (5 g.), toluene-*p*-sulphonic acid (0·026 g.), and acetic acid (15 ml.) were kept at 80° for 1 hr. Ethanol (60 ml.) was added and the mixture was cooled and kept at 0° for 1 hr. The product (3·7 g.; m. p. 110—112°) was filtered off and washed with light petroleum (b. p. 60—80°). Recrystallisation from chloroform–ethanol gave *bisdiphenylmethyl peroxide* as colourless needles, m. p. 112—113° (Found: C, 85·1; H, 6·0. $C_{26}H_{22}O_2$ requires C, 85·2; H, 6·1%). The purity of the diphenylmethanol was a critical factor in this preparation, traces of impurities presumably being able to catalyse the formation of bisdiphenylmethyl ether.

Decomposition of Bisdiphenylmethyl Peroxide in Nitrobenzene (*Table* 1).—(a) *At* 210°. The peroxide (10·00 g.) in nitrobenzene (400 ml.) was boiled under reflux for 24 hr. The solution, which had become dark red after 30 min., was extracted with sodium hydroxide (7N; 4 × 50 ml.) and with water. The aqueous extracts on being worked up for acid gave a black, unidentified oil (1·063 g.). The nitrobenzene solution was then extracted with hydrochloric acid (4N; 4 × 50 ml.) and then with water. Working-up of the aqueous portion gave

[7] Finar, " Organic Chemistry," Longmans, London, 1951, p. 541.
[8] Ward, *J.*, 1927, 2285.
[9] Davies, Foster, and White, *J.*, 1953, 1541.
[10] Hercules Powder Co., U.S.P. 2,668,180.

XUM

a basic oil (0·096 g.), which was shown to be aniline by the formation of benzeneazo-β-naphthol, m. p. and mixed m. p. 129°.

The nitrobenzene solution was reduced to 70 ml. by distillation through a 10 in. helix-packed column, and filtered through an alumina column, followed by elution with benzene (100 ml.) and ether (150 ml.). The mixed solvents were then distilled off (10 in. column). The residue was distilled to give an orange liquid (8·124 g.; b. p. 100—150°/0·4 mm.) and a residue (0·102 g.). Redistillation gave two fractions: (i) 7·865 g.; b. p. 98—120°/0·4 mm.; (ii) 0·249 g.; b. p. 128—160°/0·4 mm. Fraction (i) solidified when seeded with a crystal of benzophenone. A portion (1·179 g.) of homogenised fraction (i) on chromatography, and elution with benzene followed by ethanol, gave an orange semi-solid fraction (0·329 g.) followed by benzophenone (0·796 g.) and diphenylmethanol (0·022 g.), whose identities were established by mixed m. p.s and infrared spectra. The infrared spectrum of the first fraction from the chromatography indicated that it was largely benzophenone. The extra peaks in the spectrum corresponded to those of a mixture of nitrodiphenyls of the same isomeric composition as that produced by the decomposition of benzoyl peroxide in nitrobenzene. Comparison of the spectrum of the first fraction with those of mixtures of benzophenone and isomeric nitrodiphenyls of known composition confirmed the composition of the fraction, and established that the diaryls were present to the extent of 2% by weight of the first distillate.

Fraction (ii), on recrystallisation from chloroform–ethanol, gave a pale yellow solid, m. p. 148—153° (Found: C, 58·2; H, 3·9%), which could not be identified.

(b) *At* 115°. The above experiment was repeated in a thermostat. The results were qualitatively the same, with the exception that no nitrodiphenyls were detected.

Decomposition of Bisdiphenylmethyl Peroxide in iso*Propylbenzene.*—The peroxide (2·502 g.) was boiled under reflux in *iso*propylbenzene (100 ml.) for 7 days. The reaction mixture was extracted with sodium hydroxide (4N; 3 × 25 ml.) and with water (1 × 25 ml.). The aqueous extracts were washed with benzene (1 × 25 ml.) which was combined with the cumene solution. The aqueous layer was worked up for acid content, but contained only a trace. The organic solution was distilled at atmospheric pressure (10 in. column) leaving a residual oil which was distilled to give the following fractions: (i) 0·042 g., b. p. <85°/0·1 mm.; (ii) 2·808 g., b. p. 85—125°/0·1 mm., and a residue (0·004 g.). Fraction (i) was acetophenone [2 : 4-dinitrophenylhydrazone (m. p. and mixed m. p. 250°) and infrared spectrum]. Fraction (ii) was redistilled to give (iii) a colourless oil, 2·744 g., b. p. 94°/1 mm., (iv) a yellow solid, 0·061 g., b. p. 87—118°/0·05—0·1 mm., and a residue (0·001 g.). Fraction (iv) was bisdiphenylmethyl ether (m. p. and mixed m. p. 108°, infrared spectrum). Fraction (iii) was investigated as follows: a portion (1·371 g.) was dissolved in nitromethane (1 ml.) and cooled to −5°. The precipitated solid (0·077 g.) which was collected, washed with nitromethane and dried, had m. p. 115—117°, undepressed on admixture with 2 : 3-dimethyl-2 : 3-diphenylbutane (di-α-cumyl). The nitromethane filtrate and washings were evaporated and the residue was chromatographed. Elution with light petroleum (b. p. 40—60°) gave di-α-cumyl (0·07 g., m. p. and mixed m. p. 110—112°). Elution with light petroleum (b. p. 60—80°) and benzene gave benzophenone (0·872 g., m. p. and mixed m. p. 47°), and with ethanol gave diphenylmethanol (0·304 g., m. p. and mixed m. p. 64°).

The presence of acetophenone indicated that decomposition of cumene, by way of α-cumyl hydroperoxide, had occurred. Decomposition of this hydroperoxide would also give rise to free radicals, which would in turn produce α-cumyl radicals, by attack on cumene, and eventually di-α-cumyl by subsequent dimerisation. The experiment was, therefore, repeated at 115° in duplicate, the reaction mixtures being kept under nitrogen in the dark, in order to minimise the formation of α-cumyl hydroperoxide. The results were qualitatively the same, except that no bisdiphenylmethyl ether was detected or isolated, traces of acetophenone were detected, and a trace of unidentified colourless solid (m. p. 152—166°) was isolated from the residue.

The results are shown in Table 1.

Decomposition of Bisdiphenylmethyl Peroxide in Bromobenzene in the Presence of p*-Benzoquinone.—p*-Benzoquinone (m. p. 115°) was purified by steam distillation and crystallisation from light petroleum (b. p. 60—80°). The peroxide (6·089 g.) and benzoquinone (5·397 g.; 1½ equiv.) in bromobenzene (200 ml.) were boiled under reflux in a darkened flask for 137 hr. The black mixture was cooled (−30° for 4 hr.) and the black precipitate was collected, washed with light petroleum (b. p. 40—60°), and dried (3·4 g., m. p. 152—159°). A portion (0·426 g.) was sublimed at 135°/20 mm. for 30 hr. and the product (0·262 g.) was recrystallised from

XUM

ethanol to give quinhydrone (m. p. and mixed m. p. 170—171°). The original black material therefore contained quinhydrone (61%). Hence the recovery, based on 100% yield of hydrogen atoms from the peroxide, was 58%.

The bromobenzene solution was concentrated by distillation and the residue distilled to give two fractions: (i) b. p. 88—95°/0·1 mm.; 4·239 g., (ii) a pale yellow solid, b. p. 142—150°/0·1 mm., 0·389 g., and a residue, 1·360 g. Fraction (i) was a stable red liquid which, when seeded with benzophenone, solidified, the resultant solid rapidly darkening. The solid, in spite of the colour, had m. p. 44°, undepressed on admixture with benzophenone, and its spectrum was identical with that of pure benzophenone. It has been recorded that the colours of certain indicators dissolved in benzophenone appear only on solidification,[11] and the above remarkable colour change might be a phenomenon of this type. Fraction (ii) could not be identified.

Decomposition of Bisdiphenylmethyl Peroxide in Ethanolic Sodium Ethoxide.—Sodium (1·00 g.) in ethanol (50 ml.) was boiled under reflux to expel hydrogen. The peroxide (1·019 g.) was then added and the mixture boiled for 15 hr. The brown solution was concentrated and the residue was treated with ether (30 ml.) and water (50 ml.). After separation, the aqueous layer was extracted with ether. The combined ether extracts, on evaporation, left a brown solid (1·051 g.), a portion (0·441 g.) of which was chromatographed. Elution with light petroleum and light petroleum (b. p. 60—80°)–benzene (1 : 1) gave an unidentified yellow oil (0·022 g.). Elution with benzene gave benzophenone (0·057 g., m. p. and mixed m. p. 44°, identical infrared spectra), and ethanol gave diphenylmethanol (0·340 g., m. p. and mixed m. p. 62°).

Reaction of Benzophenone with Ethanolic Sodium Ethoxide.—Benzophenone (0·501 g.) was added to a boiling solution of sodium (1·00 g.) in ethanol (50 ml.), and the mixture was boiled for 15 hr. The mixture was worked up as described in the previous experiment to give diphenylmethanol (77%) and benzophenone (21%). A correction to the yield of benzophenone obtained from the decomposition of bisdiphenylmethyl peroxide in ethanolic sodium ethoxide could thus be made.

Decomposition of Bisdiphenylmethyl Peroxide in Pyridine.—A solution of the peroxide in pyridine was boiled under reflux (see Table 2) and the excess of solvent distilled off through a 10 in. helix-packed column. The residue was dissolved in benzene and basic material was extracted with hydrochloric acid. Concentration of the benzene solution gave a residue, which was chromatographed. Elution with light petroleum, benzene, and ethanol gave fractions which were identified by mixed m. p. and infrared spectrum. The main products were benzophenone and diphenylmethanol, although bisdiphenylmethyl ether was isolated in some cases. The pyridine and peroxide were rigorously purified in each case, but inconsistent results were obtained with this solvent. A complementary experiment, in which a pyridine solution of diphenylmethanol was boiled under reflux, indicated that benzophenone and the ether were formed, but in yields too low to account for the discrepancies. Pyridine 1-oxide was not isolated or detected.

Decomposition of Bisdiphenylmethyl Peroxide in 2 : 6-Lutidine.—A solution of the peroxide (2·987 g.) in 2 : 6-lutidine (100 ml.) was held at 115° for 8 days. Working up by the standard procedure gave benzophenone (1·22 moles/mole of peroxide) and diphenylmethanol (0·73 mole/mole of peroxide), *i.e.*, 98% recovery. No products of attack of the side-chains by free radicals were detected.

Chromatography of Bisdiphenylmethyl Peroxide.—The peroxide (0·018 mole) was adsorbed on alumina and eluted with benzene to give benzophenone (0·017 mole; m. p. and mixed m. p. 46°). Elution with chloroform gave diphenylmethanol (0·017 mole; m. p. and mixed m. p. 61—64°).

The authors gratefully acknowledge the gift of 86% hydrogen peroxide by Messrs. Laporte Chemicals Ltd., Luton. This work was carried out during the tenure (by W. A. S.) of a Peter Spence Fellowship.

KING'S COLLEGE (UNIVERSITY OF LONDON),
STRAND, LONDON, W.C.2. [*Received, July 24th*, 1958.]

[11] Terenin and Karyakin, *Doklady Akad. Nauk S.S.S.R.*, 1949, **68**, 345.

909. *Alkaline Degradation of Polysaccharides. Part V.* Periodate Oxycellulose.†*

By D. O'Meara and G. N. Richards.

Earlier work on the alkaline degradation of simple analogues has been extended to periodate oxycellulose. Identification of glycollic and αγ-dihydroxybutyric acid as the predominant soluble acidic products is interpreted as evidence that the original scission of the polymer occurs mainly by β-alkoxycarbonyl elimination at the $C_{(5)}$–O group of the origina lanhydroglucose unit. There is also some evidence that a Cannizzaro rearrangement may occur, with formation of acidic polysaccharides.

The degradation of carbonyl oxycelluloses is of considerable technological importance since it is responsible for the tendering of oxidised cellulose fabrics during scouring, laundering, or similar mild alkaline treatments. Since periodate oxycellulose is the only type of oxidised cellulose available which approaches chemical uniformity it is the most suitable material for this work. Previous studies [1-3] of the alkaline degradation of periodate oxycellulose have yielded no conclusive evidence of the mechanism of degradation. Several types of interpretation have been advanced [1-9] for the rapid depolymerisation which is known [1] to occur under mild alkaline conditions, but two theories in particular have predominated. First, Pacsu [3] likened the structure of the enol of periodate oxycellulose to a hydroxy-keten acetal and so interpreted the alkaline scission reaction as a hydroxy-keten acetal hydrolysis, yielding, ultimately, erythrose and glycollic acid from an oxidised anhydroglucose unit. This theory, as proposed, is inconsistent with Head's isolation [2] of glyoxal from the alkaline degradation of both periodate oxycellulose and periodate-oxidised methyl β-D-cellobioside. Secondly, Haskins and Hogsed [5] applied Isbell's β-hydroxycarbonyl-elimination mechanism [10] to periodate oxycellulose and suggested that scission of the $C_{(5)}$–O bond, by this mechanism would result in the formation of glyoxal and a tetrose, the tetrose arising from structures such as (II). However, while results with model compounds [9] recently confirmed the view that β-alkoxycarbonyl elimination from position 5 of the original anhydroglucose unit is the most likely cause of alkaline scission in periodate oxycellulose, the subsequent reactions differed from those postulated by Haskins and Hogsed. The present work was undertaken to test these conclusions by a study of the oxycellulose itself.

Preliminary study of four periodate oxycelluloses of different degrees of oxidation (0·24, 0·40, 0·80 and 1·01 moles of periodate/anhydro-glucose unit) showed that degradation in oxygen-free lime-water at room temperature was rapid, the oxycelluloses disintegrating to a powder and soluble acids being produced. The presence of glycollic acid and αγ-dihydroxybutyric acid was indicated by paper chromatography and confirmed by isolation of crystalline derivatives. The formation of volatile acids was also demonstrated.

Quantitative studies were carried out on two oxycelluloses (0·24 and 0·80 mole of periodate/anhydro-glucose unit). It was not possible to determine the rate of consumption

* Part IV, *J.*, 1958, 1204.

† Presented before the Division of Cellulose Chemistry at the 133rd Meeting of the Amer. Chem. Soc., San Francisco, California, April, 1958.

[1] Davidson, *J. Textile Inst.*, 1938, **29**, T195; 1940, **31**, T81; 1941, **32**, T109.
[2] Head, *ibid.*, 1947, **38**, T389.
[3] Pacsu, *Textile Res. J.*, 1945, **15**, 354.
[4] Kaverzneva, Ivanov, and Solova, *Bull. Acad. Sci. U.S.S.R.*, 1952, 681.
[5] Haskins and Hogsed, *J. Org. Chem.*, 1950, **15**, 1264.
[6] Corbett, Kenner, and Richards, *Chem. and Ind.*, 1953, 154.
[7] Kenner, *Chem. and Ind.*, 1955, 727.
[8] Corbett and Kenner, *J.*, 1953, 2245.
[9] O'Meara and Richards, *J.*, 1958, 1204.
[10] Isbell, *J. Res. Nat. Bur. Stand.*, 1944, **32**, 45.

of alkali directly because of sorption of cations by the oxycellulose in the initial stages of the reaction. As degradation proceeded some of the alkali redissolved. The reaction was therefore studied in two stages, first the initial reaction up to 1½ hr., at the end of which the solid residue was separated, and secondly, the final reaction involving the degradation by alkali to stability of the soluble neutral products from the initial reaction. At each stage the soluble products were separated into neutral and acidic components, and the acids were estimated and identified by methods described previously.[9]

The acids were divided into volatile and non-volatile fractions. The former were mainly formic acid, and the latter glycollic acid, αγ-dihydroxybutyric acid, and other acids which on paper chromatography had low mobility (R_F 0—0·20) and may include the products of Cannizzaro rearrangements of oxidised anhydroglucose units, such as were detected with model compounds.[9] The results are summarised in the Table.

Degradation of periodate oxycelluloses in 0·045N-*lime-water at* 20°.

	Yield (per g. of oxycellulose)					
	A			B		
Products	Initial	Final	Overall	Initial	Final	Overall
Insoluble residue (g.)	0·67	—	0·67	0·13	—	0·13
Neutral products (g.)	0·25	0·06	0·06	0·39	0·06	0·06
Acidic products (*milliequiv.*)						
Formic acid	0·12	0·10	0·22	0·43	0·20	0·63
Other volatile acids	0·05	0·05	0·10	0·11	0·10	0·21
Glycollic acid	0·40	0·26	0·66 (53%) †	0·97	0·90	1·87 (46%) †
αγ-Dihydroxybutyric acid	0·19	0·10 *	0·29 (23%) †	0·68	0·51	1·19 (29%) †
Acids of low mobility *	0·08	0·11	0·19	0·78	0·40	1·18
Total acids	0·84	0·62	1·46	2·97	2·11	5·08

A, B: Periodate oxycelluloses, IO_4^-/anhydro-glucose unit, 0·24 and 0·80 respectively.
* Includes other acids and lactones not separately identified.
* R_F, 0—0·20, solvent *a*.
† Percentage of theoretical maximum yield, after allowance for losses in paper chromatography.

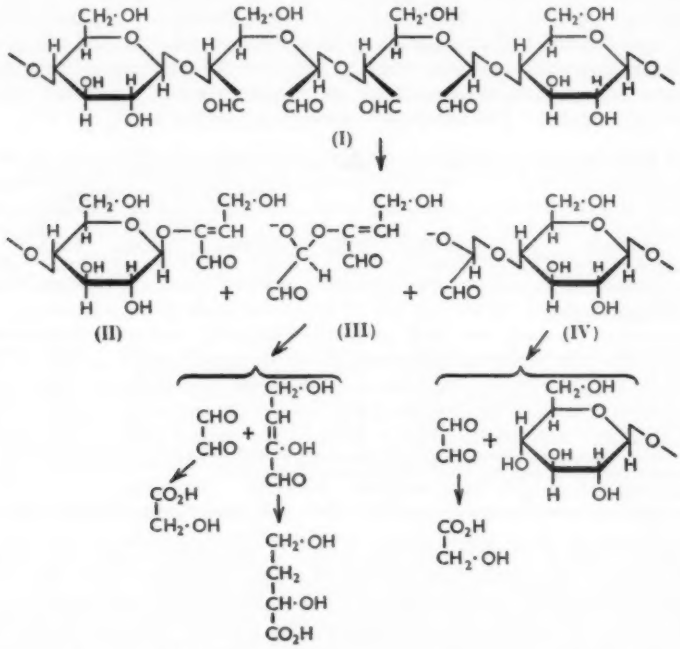
From these results it is clear that the extent of degradation depends on the original degree of oxidation, and the low final yield of neutral products shows that degradation proceeds almost completely to give acids amongst which glycollic and αγ-dihydroxybutyric predominate. The products of low chromatographic mobility formed a smaller proportion of the soluble acids from the less highly oxidised cellulose. This may be partly due to the fact that at low degrees of oxidation the products of Cannizzaro rearrangement, whose formation does not involve chain scission, are increasingly included in the insoluble residue, which was in fact shown to contain acidic groups.

On the basis of the mechanisms of alkaline degradation of periodate oxycellulose put forward by Pacsu [3] and Head [2] erythrose was predicted as one of the primary products, the other product being either glycollic acid (Pacsu [3]) or glyoxal (Head [2]). Head pointed out that except under very mildly alkaline conditions glyoxal would be rapidly converted into glycollic acid and thus, under the conditions used in the present work, both of these mechanisms predict glycollic acid and erythrose as degradation products. Similarly in the view of Haskins and Hogsed [5] the expected products would be glycollic acid and a tetrose. However, it has been shown that the main products resulting from chain-scission of periodate oxycellulose are glycollic and αγ-dihydroxybutyric acid, and since alkaline degradation of erythrose does not give high yields of αγ-dihydroxybutyric acid [11] this is not in accord with any of the above hypotheses.

By analogy with the simple model compounds previously studied [9] these results may however be interpreted as shown (I ⟶ II, etc.). Neglecting end-units the three possible types of primary product, resulting from β-alkoxycarbonyl elimination in any partially oxidised periodate oxycellulose are (II), (III), and (IV). The results of work with model compounds [9] and also an investigation of the properties of glyoxal hemiacetals [11] suggest

[11] O'Meara, unpublished results.

that an intermediate of type (III) will readily break down in lime-water at room temperature as shown, yielding equivalent amounts of glycollic and αγ-dihydroxybutyric acids. The intermediate (IV) would similarly be expected to break down readily as shown to yield glycollic acid and a normal, non-reducing glucose end unit. In the case of an intermediate of type (II) however, the α-alkoxycarbonyl group would not be expected to undergo further rapid alkaline degradation under these conditions [12] and compound (II) would therefore



accumulate and possibly ultimately degrade by other mechanisms. The lower yield of αγ-dihydroxybutyric than of glycollic acid may be partly explained on this basis, particularly since the relative proportion of the αγ-dihydroxybutyric acid is greater at higher extent of oxidation, contribution from intermediates of type (II) being then reduced. However, the yields of both glycollic and αγ-dihydroxybutyric acid are very much lower than theoretical and although the reactions shown may be regarded as the predominant mechanism of alkaline scission of periodate oxycellulose, alternative mechanisms, which would produce the same type of depolymerisation, cannot be excluded on the present evidence. In particular Pacsu's keten acetal mechanism [3] is of interest since contribution from this type of reaction would also explain the excess of glycollic over dihydroxybutyric acid.

No explanation for the formation of formic acid is offered.

Experimental

The following solvents and sprays were used for paper chromatography (cf. ref. 9) on Whatman No. 1 paper at 25°: solvents; *a*, ethyl acetate–acetic acid–water (10 : 1·3 : 1), *b*, butan-1-ol–pyridine–benzene–water (4 : 2 : 1 : 1). Sprays; *a*, " B.D.H " 4·5 indicator; *b*, permanganate–periodate; *c*, silver nitrate–sodium hydroxide.

Total acids, volatile acids, and glycollic acid were determined as described previously.[9]

[12] Kenner and Richards, *J.*, 1956, 2921.

Preparation of Periodate Oxidised Cellulose.—Chemically untreated Sudan-Sakel cotton in in the form of carded sliver was boiled gently with 2% aqueous sodium hydroxide (40 ml./g.) for 16 hr., filtered off, washed with water until free from alkali, then with acetone, alcohol, and ether, and dried *in vacuo* at 20°. The dry, scoured cotton was oxidised by 0·1M-sodium metaperiodate (100 ml./g.), reaction being followed by titration of an aliquot portion (1·0 ml.) with sodium thiosulphate.[9] When the desired degree of oxidation had taken place, the oxycellulose was washed thoroughly and dried as above.

Alkaline Degradation of Periodate Oxycellulose.—(i) *Periodate-oxidised cellulose* (*oxidised*: 0·80 *mole of periodate/anhydroglucose unit*). The oxidised cellulose (5·0 g.) was stirred with oxygen-free 0·045N-lime-water (3·0 l.). The cellulose disintegrated (*ca.* 15 min.), leaving a fine, fibrous insoluble residue. After 1½ hr., when the apparent consumption of alkali, measured by back-titration of an aliquot portion of the solution after addition of excess of acid, was 42 milliequiv., the reaction was stopped with excess of carbon dioxide. The mixture was filtered (filtrate F), the solid residue (2·51 g.) being subsequently suspended in water (50 ml.), washed free from some calcium carbonate and absorbed calcium hydroxide by dilute hydrochloric acid and then treated with lime-water to neutralise the acidic groups. The residual solid (0·65 g.) (Found: Ca, 0·8%) was filtered off, washed, and dried. The main filtrate (F), after concentration to *ca.* 600 ml. and removal of precipitated calcium carbonate, was separated into neutral and acidic components by means of the Amberlite resins IR-120(H) and IRA-400 (carbonate form) as described earlier.[9] The neutral material (N) (1·95 g.) was obtained as an amorphous powder, and the acids were obtained as a solution of their ammonium salts. An aliquot portion of the latter solution was used in the determination [9] of the total acids (14·9 milliequiv.), volatile acids (2·7 milliequiv.), and formic acid (2·15 milliequiv.), the presence of acetic acid being shown by a qualitative test.[13] Quantitative paper chromatography of a portion of the free acids [9] (1·94 milliequiv.) (solvent *a*) resulted in the isolation of glycollic acid (0·50 milliequiv.). αγ-dihydroxybutyric acid (including lactone) (0·35 milliequiv.), and acids of low mobility (R_F 0—0·15) (0·4 milliequiv.). Thus, after allowance for guide strips and volatile acids, the recovery was 86%.

The neutral material (N) (1·95 g.) was dissolved in water (50 ml.), mixed with oxygen-free 0·04N-lime-water (1 l.), and kept until alkali uptake ceased (11 days). Excess of carbon dioxide was then added, and the mixture concentrated to *ca.* 300 ml., filtered free from calcium carbonate and by means of Amberlite resins IR-120(H) (25·0 ml.) and IRA-400 (carbonate form; 25·0 ml.) in the usual way [9] was separated into neutral components (0·30 g.) and acidic components, the latter being recovered as the ammonium salts. Quantitative examination of the acids, as described above, gave total acids (10·5 milliequiv.), volatile acids (1·5 milliequiv.), and formic acid (1·17 milliequiv.). Paper-chromatography of the free acids (1·5 milliequiv.) resulted in the isolation of glycollic acid (0·45 milliequiv.), αγ-dihydroxybutyric acid (0·25 milliequiv., including lactone), and acids of low mobility (R_F 0·15) (0·2 milliequiv.), the recovery, after allowance for volatile acids and guide strips, being 78%. At each stage the glycollic acid was characterised as its 4-bromophenacyl ester, m. p. and mixed m. p. 138—140°, and the αγ-dihydroxybutyric acid as its brucine salt, m. p. and mixed m. p. 168—170°.

(ii) *Periodate-oxidised cellulose* (*oxidised*: 0·24 *mole of periodate/anhydroglucose unit*). The oxycellulose (5·0 g.) was stirred with 0·04N-calcium hydroxide (1·5 l.). After 90 min. the reaction was stopped by addition of excess of carbon dioxide. The solid residue was washed with dilute hydrochloric acid and then lime-water, dried, and weighed (3·25 g.) (Found: Ca, 0·8%). The main filtrate was then separated into neutral and acidic components as described above. The neutral material was obtained as an amorphous powder (N′) (1·26 g.), and the acids as a solution of their ammonium salts. Quantitative estimation of the acids gave total acids (4·25 milliequiv.), volatile acids (0·85 milliequiv.), and formic acid (0·59 milliequiv.). By quantitative paper chromatography of a portion of the acids (1·69 milliequiv.), glycollic acid (0·65 milliequiv.), αγ-dihydroxybutyric acid (0·31 milliequiv.), and acids of low mobility (R_F 0—0·18) (0·13 milliequiv.) were isolated. Recovery was 87%. The neutral material (N′) (1·26 g.) was treated with 0·044N-calcium hydroxide (250 ml.) at room temperature until alkali stability was reached. The mixture was treated as described above and yielded a neutral syrup (0·30 g.), together with acids, quantitative estimation of which gave total acids (3·1 milliequiv.), volatile acids (0·77 milliequiv.), and formic acid (0·52 milliequiv.). Quantitative paper chromatography of a portion of the acids (1·5 milliequiv.) resulted in the isolation of

[13] Feigl, "Spot Tests in Organic Analysis," Elsevier, Amsterdam, 1956, 5th Edn., p. 342.

glycollic acid (0·40 milliequiv.), αγ-dihydroxybutyric acid contaminated with very small amounts of other acids and lactones (0·16 milliequiv.), and acids of low mobility (R_F 0—0·20) (0·17 milliequiv.). Recovery was 73%.

This work forms part of a programme of fundamental research undertaken by the Council of the British Rayon Research Association.

THE BRITISH RAYON RESEARCH ASSOCIATION,
HEALD GREEN LABORATORIES,
WYTHENSHAWE, MANCHESTER, 22. [*Received, July 24th*, 1958.]

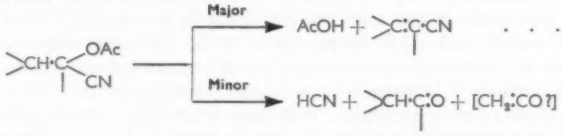
---

910. *Studies in Pyrolysis. Part XIII.* Competitive Alkyl–Oxygen and Acyl–Oxygen Scission in the Pyrolysis of Esters; αα-Disubstituted Cyanomethyl Carboxylates.*

By R. N. BENNETT, A. A. DEANS, J. G. H. HARRIS, P. D. RITCHIE, and J. S. SHIM.

New evidence, coupled with a survey of the literature, shows that the well-known alkyl–oxygen scission of carboxylic esters to carboxylic acid plus alkene (vapour phase, *ca.* 400—500°) occurs in competition with a less familiar acyl–oxygen scission by what is essentially a retro-Tishchenko reaction. The molar ratio of these two primary routes can vary over a wide range, with alkyl–oxygen and acyl–oxygen scission as the extreme limiting cases. Factors governing the balance between them are discussed, and the occurrence of further competitive reactions is briefly noted.

BURNS, JONES, and RITCHIE [1] showed that pyrolysis of 1-cyanoethyl, 1-cyano-1-methylethyl, and 1-cyano*cyclo*hexyl acetate (vapour phase, *ca.* 450—550°) leads chiefly to acetic acid plus olefinic nitrile, by alkyl–oxygen scission (A^1). Although the yields are high (*ca.* 90%), these major products are accompanied by minor by-products (hydrogen cyanide and a carbonyl compound—acetaldehyde, acetone, or *cyclo*hexanone respectively). To account for this, the following pair of competitive breakdown routes was suggested by Burns *et al.*,[1] although the formally possible third component from the minor route (keten) was not actually identified:



At the time, the mechanism of the minor competitive route was not further considered. More recently, however, Bennett, Jones, and Ritchie [2] have shown that the dicyano-substituted esters (I; R = Me or Ph), which are dimers of the corresponding acyl cyanides (II) and one of which lacks the β-hydrogen atom necessary for A^1 scission, break down pyrolytically by several competitive routes, including the following minor reversion (B^2) to monomer:

(I) $R{\cdot}CO_2{\cdot}CR(CN)_2 \longrightarrow 2R{\cdot}CO{\cdot}CN$ (II) . . . . . B^2

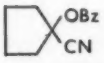
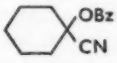
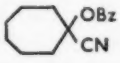
In addition, the monomer (II) breaks down further to carbon monoxide and the corresponding nitrile; where R = Me, there is also a minor competitive scission to keten and hydrogen cyanide.

* Part XII, *J.*, 1957, 4700.

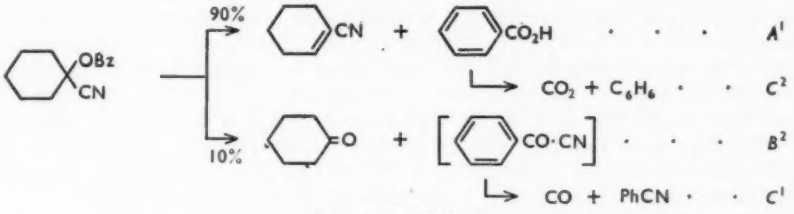
[1] Burns, Jones, and Ritchie, *J.*, 1935, 400, 714.
[2] Bennett, Jones, and Ritchie, *J.*, 1956, 2628.

Clearly, these facts suggest a fuller and more precise interpretation of the earlier results,[1] namely, that there is here a primary competition between alkyl–oxygen and acyl–oxygen scission (the former predominating), with subsequent secondary breakdown of some of the primary products. To test the general validity of this concept, six further 1-cyanoalkyl and 1-cyano*cyclo*alkyl esters (III—VIII) have now been studied:

(III) BzO·CMe$_2$·CN (IV) BzO·CMeEt·CN (V) AcO·CMeEt·CN

(VI)  (VII)  (VIII) 

The results fully confirm the idea of competition between A^1 and B^2 scissions where both are structurally permissible. All six esters, which each contain at least one β-hydrogen atom, undergo a major A^1 scission (*ca.* 90%) with a competing minor B^2 scission (up to *ca.* 10%). At the high temperatures used (*ca.* 500°), acyl cyanide from the B^2 reaction is too unstable to survive in the pyrolysate, but in each case its known breakdown products [2] are observed, sometimes together with further minor secondary products. The following example is typical of the overall results observed at 500°; the yields are only approximate, allowance being made for losses (cf. Table 1).



(*plus a trace of* HCN)

Discussion

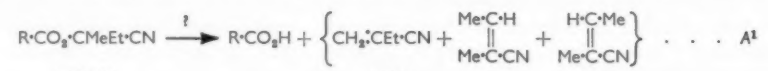
Early work on pyrolysis of carboxylic esters (well summarised to about 1928 by Hurd [3]) was rather unsystematic, and the results were too varied and apparently inconsistent for any broad generalisations owing to the use of widely varying techniques and to the tendency to concentrate on major products, without seeking (or at least recording) by-products. For example, part of the work of Burns *et al.*[1] was later repeated by Dvořák,[4] who was apparently unaware of the previous studies; but, although he too noted the major A^1 scissions, he recorded no by-product.

Significant by-products from ester pyrolyses have now been so frequently recorded (see, *inter al.*, Hurd and Blunck,[5] Ritchie *et al.*[2,6,7]) that it has gradually become apparent that in general carboxylic esters tend to break down thermally by two or more competitive primary routes. Though much remains to be done, it is becoming possible to sketch the framework of a comprehensive generalisation; an important part of this is the competition between alkyl–oxygen and acyl–oxygen scission.

Alkyl–Oxygen Scission (A^1).—Where the alkyl group contains at least one β-hydrogen atom, the well-known scission to carboxylic acid plus alkene often predominates overwhelmingly. Hurd and Blunck [5] suggested a cyclic hydrogen-bonded transition state (six-membered), a concept also applied later [8] to the analogous Tschugaeff scission of alkyl xanthates; it now seems quite widely accepted that A^1 scission proceeds *via* a concerted

[3] Hurd, "The Pyrolysis of Carbon Compounds," Chemical Catalog Co., New York, 1929, Chap. 17.
[4] Dvořák, *Coll. Trav. chim. Tchécosl.*, 1950, **15**, 907.
[5] Hurd and Blunck, *J. Amer. Chem. Soc.*, 1938, **60**, 2419.
[6] Allan, Forman, and Ritchie, *J.*, 1955, 2717.
[7] Mackinnon and Ritchie, *J.*, 1957, 2564; Allan, McGee, and Ritchie, *J.*, 1957, 4700.
[8] Stevens and Richmond, *J. Amer. Chem. Soc.*, 1941, **63**, 3132.

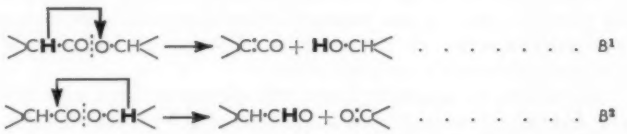
version of the Hurd and Blunck intermediate, that is to say, by a reaction " in which only one transition state separates reactants and products, all bond-making and -breaking processes occurring simultaneously." [9] At about 300° the vapour-phase reaction appears to be unimolecular and homogeneous, provided that the reaction vessel has been " seasoned " by previous runs [*e.g.*, for *tert.*-butyl formate,[10] acetate,[11] and propionate,[12] and for (−)-menthyl benzoate [13]]. The last-named ester has been shown, in one of the most careful quantitative studies in this field,[13] to follow the A^1 route exclusively, at least up to *ca.* 320°. Here, the olefinic product is a mixture of two isomeric (+)-menthenes (Δ^2 and Δ^3), a reflection of the fact that elimination may occur in two different directions. This dual condition also holds for the two 1-cyano-1-methylpropyl esters (IV, V); here the work of Bailey *et al.*[14] suggests that if the reaction vessel is clean the favoured (perhaps exclusive) olefinic product should be α-ethylacrylonitrile (IX), whereas formation of tiglonitrile (X) and/or angelonitrile (XI) should be favoured by carbonisation on the vessel wall.



(IV, V) (IX) (X) (XI)

In a related study, Bruylants *et al.*[15] have shown that a mixture of the three isomeric nitriles (IX—XI) is obtained, with (XI) predominating, when ethyl methyl ketone cyanohydrin is dehydrated *directly* (*e.g.*, by heating with phosphoric oxide). In the present work on *indirect* (pyrolytic) dehydration, the main object was simply to seek evidence for B^2 scission, and the major A^1 products were not examined in great detail, but there is some evidence that nitriles (IX) and (X) are both formed, though no evidence for angelonitrile (XI). This may mean that (XI) is not a primary scission product; alternatively, it may indicate secondary thermal isomerisation of (XI) to (X), in agreement with the known [16] geometrical inversion of angelic acid to the more stable tiglic acid on heating.

Acyl–Oxygen Scission (B^1 *and* B^2).—Because it is so often masked by a greatly preponderating A^1 reaction, acyl–oxygen scission has hitherto been almost overlooked as a minor competitive route, though it has been recorded as the sole (or at least major) route in a few cases when the A^1 reaction is precluded by the absence of a β-hydrogen atom. There are two variations [6] of acyl–oxygen scission, which may be designated the *acyl* ⟶ *alkoxyl* (B^1) and *alkoxyl* ⟶ *acyl* (B^2) types, to indicate the direction of migration of an α-hydrogen atom, thus:



Reaction B^1 has been observed for certain very thermostable esters such as phenyl,[5] *iso*propenyl,[7] and *cyclo*hex-1-enyl [7] acetate, where the only mobile α-hydrogen atom available for migration occurs in the acyl group, and the hydroxy-product may be either stable or a labile enol. Reaction B^2 has been recorded for certain methyl esters (*e.g.*, formate,[17] acetate,[18] and phenylacetate [5]) and for benzyl benzoate,[19] in the first three

[9] Cram, " Steric Effects in Organic Chemistry " (Ed. Newman), Wiley, New York, 1956, Chap. 6.
[10] Gordon, Price, and Trotman-Dickenson, *J.*, 1957, 2813.
[11] Rudy and Fugassi, *J. Phys. Colloid Chem.*, 1948, **52**, 357.
[12] Warrick and Fugassi, *ibid.*, 1948, **52**, 1314.
[13] Barton, Head, and Williams, *J.*, 1953, 1715; cf. also *idem*, *J.*, 1952, 453.
[14] Bailey *et al.*, *J. Amer. Chem. Soc.*, 1955, **77**, 73, 75, 357.
[15] Bruylants, Ernould, and Dekoker, *Bull. Soc. chim. Belg.*, 1925, **37**, 562.
[16] Blaise, *Ann. Chim. Phys.*, 1907, **11**, 111.
[17] Muller and Peytral, *Compt. rend.*, 1924, **179**, 831; Peytral, *Bull. Soc. chim. France*, 1925, **37**, 562.
[18] *Idem*, *ibid.*, 1922, **31**, 118.
[19] Hurd and Bennett, *J. Amer. Chem. Soc.*, 1929, **51**, 1197.

XUM

cases competing at rather high temperatures (*ca.* 600° and upwards) with other primary routes. It is, furthermore, the *sole* recorded breakdown-route, at only *ca.* 200—300°, of certain trichloroacetates [20] (*e.g.*, benzyl and phenethyl), in which the highly electronegative trichloromethyl group markedly weakens the acyl–oxygen bond, even to the extent of excluding completely the A^1 scission expected of the phenethyl ester. An allied acyl–oxygen scission is the reversion [21] of dimeric carbonyl chloride (trichloromethyl chloroformate) to its monomer, at only *ca.* 300°. This demonstrates an interesting migration of α-chlorine, where no α-hydrogen is available.

It is possible, though as yet unproven, that routes B^1 and B^2 may be followed competitively by a single ester. For example, ethyl acetate at *ca.* 550° yields [5] a complex pyrolysate the composition of which is compatible with this idea, though A^1 scission is of course the main breakdown-route.

B^2 Scission considered as a Retro-Tishchenko Reaction.—Several of the observed routes by which esters break down thermally are equivalent to reversal of well-known addition reactions (usually catalytic) by which the pyrolysand may be produced otherwise than by normal esterification. Thus, alkyl–oxygen (A^1) and alkenyl–oxygen (A^2) scission [6, 7] constitute thermal reversal of the catalysed addition of carboxylic acid to alkene and alkyne respectively; B^1 scission is a reversal of the addition of a keten to a hydroxy-compound (which may be an enol); and, similarly, B^2 scission is a reversal of the catalysed self-addition (dimerisation) of carbonyl compounds exemplified by the Tishchenko variation of the Cannizzaro reaction.[22] Hence, since all alkyl carboxylates can formally be regarded as products of this carbonyl–carbonyl addition reaction, either simple or crossed (whether or not they can actually be synthesised thus in practice), it is reasonable to enquire whether its reversal always occurs in their pyrolysis. This idea was examined by Bilger and Hibbert [23] but rejected because they could not detect aldehydes or ketones in the pyrolysates from a series of alkyl esters; nevertheless, the evidence now summarised makes it clear that B^2 scission is one of the main competing routes in ester pyrolysis. Thus, the B^2 scission of benzyl benzoate [19] is a reversal of the simple Tishchenko reaction by which this ester can be prepared from benzaldehyde; [24] the B^2 scission of benzyl trichloroacetate [20] is, on the other hand, the reversal of a crossed Tishchenko reaction between chloral and benzoaldehyde, not apparently realised in practice.

As might be expected, there is no observable tendency for an α-alkyl group to migrate rather than the α-cyano-group during a retro-Tishchenko reaction. No alkyl phenyl ketone was observed in the pyrolysis of esters (III—V), and no opening of the ring for esters (VI—VIII), though all yielded small amounts of the appropriate purely aliphatic ketone.

Summarising, then, we say that a carboxylic ester may in principle follow at least two distinct thermal breakdown-routes, A^1 and B^2, the balance being dictated (sometimes to the effective exclusion of one route) by the presence or absence of some critical structural feature, such as a mobile hydrogen atom or a highly polar group. It is clear, for example, from the wide variety of temperatures required to bring about the B^2 scissions listed above,[17–21] that the number and type of α-substituents in a methyl ester have a critical bearing on the result. Presumably, too, the reaction temperature itself influences the $A^1 : B^2$ ratio.

Formation of Hydrogen Cyanide from Esters (VI—VIII).—Although the various benzoates now studied cannot yield hydrogen cyanide by the same route as does the acetate (V) (*i.e.*, *via* an acyl cyanide), the esters (VI—VIII) produce a slight trace of it on pyrolysis. Its origin is uncertain. It may be due to a very minor thermal reversal of

[20] Hibbert and Greig, *Canad. J. Res.*, 1931, **4**, 254.
[21] Ramsperger and Waddington, *J. Amer. Chem. Soc.*, 1933, **55**, 214.
[22] Geissman, "Organic Reactions," Wiley, New York, 1944, Vol. II, Chap. 3; Wagner and Zook, "Synthetic Organic Chemistry," Wiley, New York, 1953, p. 494.
[23] Bilger and Hibbert, *J. Amer. Chem. Soc.*, 1936, **58**, 823.
[24] Kamm and Kamm, *Org. Synth.*, 1922, **2**, 5.

the known catalysed addition of hydrogen cyanide to alk-1-enyl carboxylates (*e.g.*, the conversion of vinyl benzoate into 1-cyanoethyl benzoate [25]). Alternatively, it may be due to a minor breakdown of the olefinic nitrile in the primary pyrolysate, by thermal reversal of the known catalysed addition of hydrogen cyanide to alkynes (*e.g.*, the conversion of acetylene into acrylonitrile [25]). A control experiment showed that acrylonitrile does, in fact, break down thus on pyrolysis, but the nitrile is very thermostable, the yield of hydrogen cyanide being only *ca.* 0·2% even at *ca.* 650°.

Other Competitive Routes.—In all the examples now described (III—VIII), the α-carbon atom of the alkyl group is fully substituted. Where, however, this is not so, and the α-carbon atom bears at least one hydrogen atom, simple competition between A^1 and B^2 scissions may be complicated by the appearance of at least two other concurrent competitive reactions. One of these (the formation of α-diketones) is of considerable novelty; the results will be described elsewhere.

Experimental

Apparatus and Procedure.—The reaction vessel, receiver, and traps, together with the mode of operation, cleaning, and flushing with nitrogen, have been described.[6] Three different flow-vessels were used, P.1 and P.2 (of Pyrex glass) and S (of stainless steel). All were packed with Pyrex tubing, the free unpacked space being 125, 50, and 80 ml. respectively.

Results.—Analytical methods. Tables 1 and 2 summarise the general conditions and results for 14 runs. Apparent overall losses in weight are due to carbonisation and/or hold-up in the packed vessel. Contact times are calculated as before.[26]

The examination of typical pyrolysates is detailed below. Hydrogen cyanide was removed from the exit gases by a cold trap, and keten (Runs 3—9) by an aniline–ether trap. Aldehydes and ketones were characterised as their 2 : 4-dinitrophenylhydrazones, benzene as *m*-dinitrobenzene, and benzonitrile by conversion [27] into benzamide by alkaline hydrogen peroxide; all solid derivatives or pyrolysis products were identified by mixed m. p.

1-*Cyano*-1-*methylethyl Benzoate* (III).—*Preparation.* Francis and Davis's [28,29] method yielded the ester as a colourless oil (42%), b. p. 184—185°/70 mm., solidifying to crystals, m. p. 36° (lit.,[29] b. p. 185—190°/70—80 mm., m. p. 35—36°).

Pyrolysis: *Run* 1. No hydrogen cyanide could be detected in (*b*). Distillation of (*a*) yielded (i) a trace of acetone, b. p. *ca.* 60°, (ii) 44 g., b. p. 70—95°, and (iii) a solid residue which frothed on attempted distillation. Fraction (ii), strongly cooled, deposited crystalline benzene; the liquid portion, decanted and fractionally distilled, yielded α-methylacrylonitrile, b. p. 91—91·5° (Found: N, 20·8. Calc. for C_4H_5N: N, 20·9%). Residue (iii), washed with aqueous sodium hydrogen carbonate, yielded 30 g. of benzoic acid; the final residue, distilled, yielded 2·0 g., b. p. 68—72°/10 mm., containing benzonitrile.

1-*Cyano*-1-*methylpropyl Benzoate* (IV).—*Preparation* (i). Equimolar quantities of ethyl methyl ketone, benzoyl chloride, and potassium cyanide (aqueous) were treated as for the ester (III). The final reaction mixture was extracted with ether; the extract was washed with sodium carbonate, dried, and distilled under reduced pressure, giving the ester (40%) as a colourless liquid, b. p. 175—180°/15 mm. (ii). Equimolar quantities of redistilled ethyl methyl ketone cyanohydrin, benzoyl chloride, and technical pyridine were heated at 100° (1 hr.) and allowed to cool; after deposition of solid (pyridine hydrochloride) the liquid was decanted off, washed in succession with brine, sodium carbonate, and hydrochloric acid, and distilled under reduced pressure. The *ester* (35%) had b. p. 175°/18 mm (Found: C, 71·0; H, 6·4. $C_{12}H_{13}O_2N$ requires C, 71·1; H, 6·4%).

Pyrolysis: *Run* 2. The pyrolysis of ester (IV) was not studied in full detail, but sufficient evidence was obtained to demonstrate qualitatively the competition between A^1 and B^2 scissions. Distillation of (*a*) yielded a trace of ethyl methyl ketone, a main liquid fraction,

[25] Kurtz, *Annalen*, 1951, **572**, 23.
[26] Allan, Jones, and Ritchie, *J.*, 1957, 524.
[27] Radziszewski, *Ber.*, 1885, **18**, 355.
[28] Francis and Davis, *J.*, 1909, **95**, 1403.
[29] Davis, *J.*, 1910, **97**, 949.

XUM

TABLE 1. *Pyrolysis of cyano-esters* (III, IV, VI, VII, VIII).

Pyrolysand, run no.	(III), 1	(IV), 2	(VI), 10 *	(VII), 11	(VII), 12 *	(VII), 13	(VIII), 14 *
Reaction vessel	S	S	P.2	P.2	P.2	P.2	P.2
Temp.	400°	510°	495°	395°	495°	555°	495°
Feed-rate (g./min.)	1·46	1·25	0·60	0·60	0·80	0·50	0·43
Contact time (sec.)	11	12	17	21	16	20	27
Wt. pyrolysed (g.)	90·7	100·0	69·0	63·0	76·0	49·0	64·0
(*a*) In main receiver (g.)	82·4	—	67·2	61·0	71·0	47·2	63·0
(*b*) Gaseous pyrolysate (l.)	5·6	0·5	1·5	—	4·0	—	1·2
Composition (%) of (*b*) (approx.):							
CO	11	Pres.	25	—	11	—	26
CO_2 †	89	Pres.	75	—	88	—	74
Unsat. hydrocarbons	Nil	—	Nil	—	1	—	Nil
Composition of total pyrolysate (approx.): ‡							
Benzoic acid	Pres.	Pres.	32·0 (84)	17·6 (57)	31·0 (82)	20·3 (81)	17·7 (56)
Olefinic nitrile	Pres.	Pres.	22·5 (78)	14·7 (54)	25·5 (77)	18·2 (83)	18·0 (58)
Ketone	Pres.	Pres.	1·2 (5)	8·7 (35)	2·0 (6)	0·8 (4)	8·6 (29)
Benzonitrile	Pres.	Pres.	1·8 (6)	9·7 (37)	1·8 (6)	0·7 (3)	7·5 (28)
Benzene	Pres.	—	3·0	Nil	0·8	0·4	0·3
Unchanged pyrolysand	—	—	Nil	2·8 (5)	Nil	Nil	Nil
Hydrogen cyanide	—	—	(0·7)	(0·1)	(0·1)	(0·2)	(0·3)
Processing losses, tars, gases, etc.	—	—	8·5	9·5	14·9	8·6	11·9

* Gas analyses done by separate runs (10 min.), at same temperature, in semimicro-reaction vessel;[33] yield of gas, 7 ml. from 0·32 g. of (VI), 10 ml. from 0·30 g. of (VII), 10 ml. from 0·30 g. of (VIII).

† Including traces of hydrogen cyanide (no alkali trap used).

‡ Figures in parentheses represent percentage yields; other figures in g.

— Not examined. Pres. = Present.

TABLE 2. *Pyrolysis of* 1-*cyano*-1-*methylpropyl acetate* (V).

Run No.	3	4	5	6	7	8	9
Reaction vessel	P.1	P.1	P.1	P.1	P.1	P.1	P.1
Temp.	425°	425°	425°	475°	475°	475°	525°
Feed-rate (g./min.)	2·0	3·3	9·7	2·5	4·4	10·9	4·4
Contact time (sec.)	9	6	2	7	4	2	4
Wt. pyrolysed (g.)	100·0	100·0	100·0	100·0	100·0	100·0	100·0
(*a*) In main receiver (g.)	99·9	99·7	99·6	88·5	95·2	98·5	91·6
(*b*) Gaseous pyrolysate (l.)	2·9	2·2	2·0	—	1·4	2·6	2·7
Composition (%) of (*b*) (approx.):							
CO	—	38	31	—	65	52	51
CO_2	—	2	Nil	—	6	1	12
Unsat. hydrocarbons	—	Nil	Nil	—	4	2	7
Sat. hydrocarbons	—	60	69	—	25	45	30
Composition (g.) of total pyrolysate (approx.): *							
Acetic acid: by titration †	40·7	41·2	37·5	—	—	39·0	39·9
by fractionation ‡	38·1	37·9	42·1	40·3	38·5	40·5	39·3
B. p. 112—116°: total	23·0	10·2	16·8	26·2	24·1	16·3	11·6
nitrile (IX)	20·2	8·6	14·4	24·0	20·8	12·3	10·0
B. p. 117—119°: total	6·8	11·9	2·8	Nil	Nil	12·5	2·1
nitriles (IX) + (X)	6·5	11·6	1·7	Nil	Nil	11·7	1·2
B. p. 120—124°: total	11·6	18·3	17·7	8·2	5·7	8·1	15·6
nitrile (X)	10·4	16·5	16·0	7·6	5·5	6·2	15·1
B. p. <92°: mostly Me·CO·Et	4·2	3·1	3·2	0·2	0·2	2·4	3·8
Unchanged pyrolysand	3·0	1·5	9·5	3·0	1·0	4·0	1·0
Hydrogen cyanide	0·01	Trace	Trace	0·02	0·01	0·01	0·01

* Excluding processing losses, tars, etc.

† By titration of aliquot portion of (*a*).

‡ Acid in brine extract (by titration) plus acid in nitrile fractions (by difference, after Kjeldahl determination of nitrile).

— Not recorded.

b. p. 110—130°, and a semi-solid residue of benzoic acid containing a trace of benzonitrile. The boiling range of the main fraction embraced the b. p.s of nitriles (IX) and (X) (114° and 122° respectively [30]); the liquid had a strong characteristic smell closely similar to that of α-methylacrylonitrile, was unsaturated, and evolved ammonia when heated with alkali, all confirming the presence of olefinic nitriles.

1-*Cyano*-1-*methylpropyl Acetate* (V).—*Preparation.* Ethyl methyl ketone cyanohydrin and acetic anhydride (equimolar) were warmed with a trace of concentrated sulphuric acid; the cooled reaction mixture was shaken with brine, and the non-aqueous layer distilled, giving pure ester (68%), b. p. 92—94°/13 mm., 198—199° (lit.,[30] b. p. 195°).

Pyrolysis: *Runs* 3—9. These runs gave qualitatively similar results (Table 2). In each run, the products were worked up in four stages. (i) Liquid (*a*) was distilled: the first volatile fraction (b. p. <50°) was added to any liquid in the cold trap, and the hydrogen cyanide content determined volumetrically. (ii) The presence of keten in the exit gases was shown by the detection of acetanilide in the aniline trap. (iii) The total free acetic acid was determined by titrating a 2 ml. sample of liquid (*a*): a control experiment showed that the presence of olefinic nitriles did not interfere with the titration. (iv) The bulk of the acetic acid was removed from liquid (*a*) by shaking with brine; the insoluble layer was dried and fractionally distilled. The plot of cumulative distillate volume against b. p. showed well-marked plateaux at *ca.* 80° (small: fraction contained ethyl methyl ketone), 112—116° [nitrile (IX) has b. p. 114°], 120—124° ([nitrile (X) has b. p. 122°], and *ca.* 200° (small: fraction mainly unchanged pyrolysand). There was no plateau at 140°, the b. p. of angelonitrile (XI).[30] The nitrile content of the fractions with b. p. 112—116° and 120—124°, and of the intermediate fraction (b. p. 117—119°) containing a mixture of nitriles, was measured *via* the nitrogen content of those fractions (Kjeldahl: concentrated sulphuric acid, with selenium catalyst): see Table 2.

1-*Cyano*cyclo*pentyl Benzoate* (VI).—*Preparation.* Aloy and Rabaut's method [31] yielded colourless prisms from ethanol (65%), m. p. 51—52° (lit.,[31] m. p. 52—53°) (Found: N, 6·9. Calc. for $C_{13}H_{13}O_2N$: N, 6·5%).

Pyrolysis 10. Distillation of (*a*) (pasty solid) yielded (i) 3·3 g., b. p. 70—96°, (ii) 0·8 g., b. p. 130—132°, (iii) 23·0 g., mostly b. p. 164—170°, (iv) 1·6 g., b. p. 170—198°, and (v) 36·0 g. of greyish crystalline residue (overall loss, 2·5 g.). Fraction (i) yielded benzene and *cyclo*pentanone; fraction (ii) yielded *cyclo*pentanone (combined yield of ketone from both fractions, *ca.* 5%); fraction (iii) yielded 1-cyano*cyclo*pentene (78%), b. p. 165—166°, which on alkaline hydrolysis gave *cyclo*pent-1-enecarboxylic acid (86% based on nitrile); fractions (iv) and (v) yielded benzonitrile (*ca.* 6%), b. p. 190—191°, and benzoic acid (84%), b. p. 115—120°/5 mm. There was no unchanged (VI). The alkali trap retained *ca.* 0·7% of hydrogen cyanide.

1-*Cyano*cyclo*hexyl Benzoate* (VII).—*Preparation.* Aloy and Rabaut's method [31] yielded colourless prisms from ethanol (70%), m. p. 73—74° (lit.,[32] m. p. 71°) (Found: C, 73·3; H, 6·7. Calc. for $C_{14}H_{15}O_2N$: C, 73·4; H, 6·5%).

Pyrolyses 11—13. These three runs gave similar results; those of Run 12 are given as typical. Distillation of (*a*) (pasty solid) yielded (i) 0·8 g., b. p. *ca.* 80° (benzene), (ii) 27 g., b. p. 84—170°, (iii) 33 g., b. p. 170—220°, (iv) 27 g., b. p. 144—148°/19 mm. (benzoic acid), and (v) 4·5 g. of residual tar (overall loss, 3·0 g.). Fraction (ii), redistilled, yielded 2·0 g., b. p. 156—157° (*cyclo*hexanone: *ca.* 6%). Fraction (iii), redistilled, yielded 1·8 g., b. p. 190—195° (mainly benzonitrile) and 25·5 g., b. p. 195—198° (mainly 1-cyano*cyclo*hexene; *ca.* 77%). The latter sub-fraction was converted by alkaline hydrolysis into *cyclo*hex-1-enecarboxylic acid (dibromo-derivative). Fraction (iii) and residue (v) yielded a further 4 g. of benzoic acid (total yield 82%). There was no unchanged (VII). The alkali trap retained *ca.* 0·1% of hydrogen cyanide.

1-*Cyano*cyclo*heptyl Benzoate* (VIII).—*Preparation.* This *benzoate* was prepared (20%) on the same lines as esters (VI) and (VII), as colourless prisms from methanol, m. p. 72·5°. Several variations in the method failed to give yields comparable with those of (VI) and (VII) (Found: C, 73·9; H, 6·8; N, 5·5. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0; N, 5·8%).

Pyrolysis 14. Distillation of (*a*) (pasty solid) yielded (i) 0·3 g., b. p. *ca.* 80° (benzene), (ii) 41 g., b. p. 176—225°, (iii) 16·5 g., b. p. 118—120°/5 mm. (benzoic acid), and (iv) 3 g. of

[30] Stull, *Ind. Eng. Chem.*, 1947, **39**, 517.
[31] Aloy and Rabaut, *Bull. Soc. chim. France*, 1918, **23**, 98.
[32] *Idem*, *Compt. rend.*, 1913, **156**, 1547.

residual tar (overall loss, 2·2 g.). Fraction (ii), redistilled, yielded a sub-fraction (20·9 g.), b. p. 178—200°, containing *cyclo*heptanone and benzonitrile. A rigorous separation of these substances proved impossible, but careful fractionation gave 8·6 g., b. p. 180—182° (mostly *cyclo*heptanone: *ca.* 29%), and 7·5 g., b. p. 192—194° (mostly benzonitrile: *ca.* 28%). Fraction (ii) yielded a further sub-fraction consisting of 1-*cyano*cyclo*heptene* (*ca.* 58%), b. p. 213—214° (Found: C, 79·6; H, 8·7. $C_8H_{11}N$ requires C, 79·3; H, 9·2%), converted by alkaline hydrolysis into *cyclo*hept-1-enecarboxylic acid. Fraction (ii) and residue (iv) yielded a further 1·2 g. of benzoic acid (total yield 56%). There was no unchanged (VIII). The alkali trap retained *ca.* 0·3% of hydrogen cyanide.

Acrylonitrile. Freshly redistilled commercial nitrile, from L. Light and Company Ltd., was used, b. p. 78—79°.

Pyrolysis 15. Preliminary runs (vessel P.2) showed that the nitrile was very thermostable at 500—600°. At 650°, 20 g. of nitrile yielded 17·3 g. of unchanged material plus 2·0 g. of high-boiling tars; an alkali trap removed hydrogen cyanide (0·2%) from the exit gases (0·4 l.), the remainder of which consisted of displaced nitrogen plus a little acetylene (infrared).

The authors thank Monsanto Chemicals Ltd. and the British Council for the award of scholarships (to R. N. B. and J. S. S. respectively). They are also indebted to Dr. E. Jones for a number of gas analyses, and for the pyrolysis of acrylonitrile.

CHEMICAL TECHNOLOGY DEPARTMENT,
ROYAL COLLEGE OF SCIENCE AND TECHNOLOGY,
GLASGOW, C.1.

[*Received, July 28th*, 1958.]

---

911. *Studies in Pyrolysis. Part XIV.* The Pyrolysis of 2 : 2-Dimethyltrimethylene Dibenzoate.*

By A. GOLOMB and P. D. RITCHIE.

In the vapour phase at *ca.* 500°, 2 : 2-dimethyltrimethylene dibenzoate undergoes primary acyl–oxygen scission to benzaldehyde and an unstable ester-aldehyde, β-benzoyloxy-αα-dimethylpropionaldehyde. The latter undergoes a secondary decarbonylation to *iso*butyl benzoate, which then breaks down by the predictable alkyl–oxygen and acyl–oxygen scissions.

POHL [1] showed that poly(ethylene terephthalate) (I) is less resistant to thermal breakdown than its higher *gem.*-dimethyl analogue (II), though no detailed mechanism was suggested. Later, an interpretation for the easier breakdown of the polyester (I) was elaborated by Ritchie *et al.*[2] from a study of the model compound ethylene dibenzoate (III) and related substances, but no consideration was then given to polyester (II). However, the increasing availability of *neo*pentylene glycol (2 : 2-dimethylpropane-1 : 3-diol), which is the key raw-material for (II), has now prompted a study of the thermal stability of its esters. *neo*Pentylene dibenzoate (2 : 2-dimethyltrimethylene dibenzoate) (IV) was selected, as constituting a good model for polyester (II); the results clarify the thermal breakdown of the latter.

$H\cdot[O_2C\cdot C_6H_4\cdot CO_2\cdot CH_2\cdot CH_2]_n\cdot OH$ (I)

$H\cdot[O_2C\cdot C_6H_4\cdot CO_2\cdot CH_2\cdot CMe_2\cdot CH_2]_n\cdot OH$ (II)

$BzO\cdot CH_2\cdot CH_2\cdot OBz$ (III)

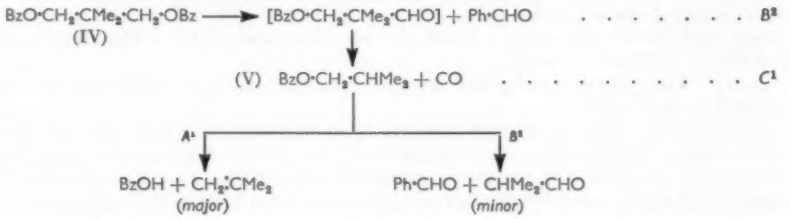
$BzO\cdot CH_2\cdot CMe_2\cdot CH_2\cdot OBz$ (IV)

The greater thermal stability of polyester (II) than of (I) finds a parallel in the behaviour of the corresponding models (IV) and (III), which under identical conditions break down at 500° (vapour phase) to the extent of *ca.* 50% and *ca.* 81% respectively (see Experimental).

* Part XIII, preceding paper.

[1] Pohl, *J. Amer. Chem. Soc.*, 1951, **73**, 5660.
[2] Ritchie *et al.*, *J.*, 1955, 2717; 1956, 3563; 1957, 524, 2107, 2556.

The absence of a β-hydrogen atom from substances (II) and (IV) precludes the A^1 scission readily undergone by substances (I) and (III), leaving as the only readily predictable breakdown-route an acyl–oxygen scission (B^2) at higher temperatures (cf. preceding paper). The nature of the complex pyrolysate from model (IV) supports this conclusion. The major products are benzaldehyde, benzoic acid, benzene, carbon monoxide, carbon dioxide,



*iso*butene, and *iso*butyl benzoate, plus traces of *iso*butyraldehyde, benzoic anhydride, and water. Other substances sought (see below), but with negative results, were formaldehyde, trimethylacetaldehyde, *iso*butylbenzene, and hydrogen. The best interpretation of the results indicates a primary non-competitive B^2 scission, followed by the secondary scissions shown in the annexed scheme (coupled with certain other simple predictable decompositions).

Discussion.—The key to the above interpretation of the analytical results is the identification of *iso*butyl benzoate (V). This can hardly originate otherwise than by decarbonylation of the ester-aldehyde β-benzoyloxy- αα-dimethylpropionaldehyde, which, though not identified, can therefore confidently be postulated as the intermediate product accompanying benzaldehyde on primary B^2 scission of ester (IV). No evidence was found that this ester-aldehyde also breaks down by other competitive routes, such as a further secondary scission to two aldehydes, benzaldehyde and dimethylmalondialdehyde. The latter is likely to be very unstable thermally, like its lower monomethyl homologue,[3] and at 500° could well yield *iso*butyraldehyde by semidecarbonylation; but, though a trace of the latter aldehyde occurs in the pyrolysate from ester (IV), it can be accounted for alternatively and with greater certainty. A separate pyrolysis of *iso*butyl benzoate (Table, Run 4) showed, as expected, predominating A^1 scission accompanied by a minor B^2 scission to benzaldehyde and *iso*butyraldehyde, a result in agreement with the by-products recorded by Hurd and Blunck [4] in the analogous pyrolysis of *iso*butyl acetate.

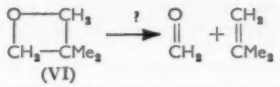
Certain other constituents of the pyrolysate may formally arise *via* more than one route. For example, A^1 scission of *iso*butyl benzoate is certainly responsible for most of the *iso*butene (which corresponds roughly in molar amount to the observed benzoic acid and its decarboxylation product, benzene), but part of the alkene may conceivably be formed in another way. Other work [5] has shown that for many esters the competitive pyrolytic routes include a disproportionation to acid anhydride plus an unstable ether; on this basis the ester (IV) might yield benzoic anhydride and the cyclic ether 2 : 2-dimethyltrimethylene oxide (VI). The present results, however, suggest that this does not occur. The pyrolytic properties of ether (VI) are not known, but its simplet analogue trimethylene oxide (VII) breaks down [6] at *ca.* 450° to formaldehyde and ethylene (with no evidence for rearrangement to propionaldehyde), which suggests that ether (VI), if formed initially at *ca.* 500°, should similarly yield formaldehyde (or its breakdown products, including hydrogen) and *iso*butene, but probably not trimethylacetaldehyde.

Formaldehyde, hydrogen, and trimethylacetaldehyde could not be detected; also, the observed trace of acid anhydride is apparently formed by direct dehydration of benzoic

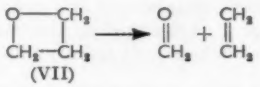
[3] Pummerer, Hahn, Johne, and Kahlen, *Ber.*, 1942, **75**, 867.
[4] Hurd and Blunck, *J. Amer. Chem. Soc.*, 1938, **60**, 2419.
[5] Jones and Ritchie, unpublished observations.
[6] Bittker and Walters, *J. Amer. Chem. Soc.*, 1955, **77**, 1429.

acid (cf. Davidson and Newman [7]), since a little water is also found. Hence, it seems that no significant amount of the observed *iso*butene arises *via* such a disproportionation.

No products attributable to primary decarboxylation of ester (IV) could be detected; for example, there was no *iso*butylbenzene, which should result from a C^2–B^2–C^1 sequence. Benzene is the only decarboxylation-product observed, though part of it is also probably formed by decarbonylation of benzaldehyde.



(VI)



(VII)

It thus appears that the pyrolysis of ester (IV) is adequately represented by the relatively simple breakdown-scheme given above, which can also be applied to elucidate the thermal breakdown of the polyester (II) studied by Pohl.[1]

Experimental

General.—The apparatus and procedure have been described.[8] The Table summarises the general conditions; the temperature was 500°; detailed analyses are given below. Aldehydes were characterised as their 2 : 4-dinitrophenylhydrazones, and benzene as *m*-dinitrobenzene; all solid derivatives or pyrolysis products were identified by mixed m. p., except in Run 4, where paper chromotography was preferred. Hydrogen and saturated hydrocarbons were absent.

2 : 2-*Dimethyltrimethylene Dibenzoate* (IV).—Prepared from 2 : 2-dimethylpropane-1 : 3-diol, benzoyl chloride, and pyridine in standard fashion (77% yield), this had m. p. 51—53° (lit.,[8] m. p. 52—54°) and b. p. 225°/9 mm., 271°/40 mm.

Pyrolysis of Ester (IV).—Runs 1 and 2 gave concordant results; those of Run 1 are given here. Liquid (*a*) from the cold trap, raised to room temperature, evolved 0·34 l. of gas, identified as *iso*butene (infrared spectrometry); benzene remained (*ca.* 2 ml.). Distillation of (*b*) yielded four primary fractions (i—iv) and a residue (v). Fraction (i) (b. p. 30—110°/40 mm.), redistilled, yielded 2·8 g. of colourless liquid, b. p. 60—90°, containing benzene and *iso*butyraldehyde, and 1·5 g. of colourless liquid, b. p. 90—150°, containing benzene and water (anhydrous copper sulphate test). Fraction (ii) (b. p. 110—160°/40 mm.), redistilled, yielded 0·5 g. of yellowish liquid, b. p. 155—175° (in which no *iso*butylbenzene could be detected by attempted Friedel–Crafts aroylation with phthalic anhydride), and 2·7 g. of yellowish liquid, b. p. 175—220°, containing mainly benzaldehyde. (No further aldehydes could be detected in the total pyrolysate.)

Pyrolysand, run no.	(IV), 1		(IV), 2		(III), 3		(V), 4	
Feed-rate (g./min.)	0·42		0·38		0·42		0·45	
Contact time (sec.)	140		150		135		82	
Wt. pyrolysed (g.)	50·0		50·0		50·0		50·0	
(*a*) In cold trap (ml.)	3·0		3·0		*X*		*X*	
(*b*) In main receiver (g.)	38·1		36·6		44·5		34·0	
(*c*) Gaseous pyrolysate (l.)* ...	4·8	CO 70% CO_2 25% Uns 5%	4·2	68% 28% 4%	3·0	— — —	—	— — —

* With approximate percentages (v/v); uns = unsaturated hydrocarbons.
X = No cold trap used.
— = Not observed. Overall losses in weight are due to carbonisation and hold-up in the vessel.

Fraction (iii) (b. p. 160—200°/40 mm.), redistilled, yielded 2·5 g. of yellow semi-solid product, b. p. 220—280°, from which hot water extracted benzoic acid; the residue, freed from benzoic acid by treatment in ethereal solution with dilute aqueous sodium carbonate, followed by removal of ether, was an oil which on hydrolysis with aqueous alkali yielded *iso*butyl alcohol (characterised as its 3 : 5-dinitrobenzoate) and benzoic acid, thus proving the presence of *iso*butyl benzoate. Fraction (iv) (b. p. 200—260°/40 mm.), redistilled, yielded 0·3 g. of crude benzoic acid, b. p. 280—300°; attempts to detect 2 : 2-dimethyl-1 : 3-diphenylpropane (b. p.

[7] Davidson and Newman, *J. Amer. Chem. Soc.*, 1952, **74**, 1515.
[8] Bincer and Hess, *Ber.*, 1928, **61**, 537.

273°) gave negative results. The residue (v) was mainly unchanged pyrolysand (*ca.* 25 g.; 50%): a portion, tested by the Davidson–Newman reagent,[7] gave a slight positive reaction for acid anhydride.

Pyrolysis of Ethylene Dibenzoate (III).—The ester was prepared as previously described:[2] under the same conditions as for ester (IV), only *ca.* 19% of the pyrolysand remained unchanged (Run 3).

Pyrolysis of iso*Butyl Benzoate* (V).—Under the same conditions (Run 4), the carefully purified ester yielded chiefly benzoic acid and *iso*butene; but the liquid pyrolysate yielded a trace of a mixture of crude 2 : 4-dinitrophenylhydrazones, shown by paper chromotography to consist of those of benzaldehyde and *iso*butyraldehyde.

The authors thank Imperial Chemical Industries Limited (Nobel Division) for a gift of *neo*pentylene glycol.

CHEMICAL TECHNOLOGY DEPARTMENT,
ROYAL COLLEGE OF SCIENCE AND TECHNOLOGY, GLASGOW, C.1. [*Received, July 28th*, 1958.]

---

912. *Sesquiterpenoids. Part XI.* The Constitution of Geigerin.*

By D. H. R. BARTON and J. E. D. LEVISALLES.

The earlier work on the constitution of geigerin has been extended. Geigerin contains a secondary hydroxyl group placed in the vinylogous α-position with respect to the ketone group. The relation between this hydroxyl group and the lactone system has been firmly established and the constitution of geigerin shown to be (III; R = H). The nature of the so-called *allo*geigeric acid has been elucidated. On the basis of the constitution of this acid and of other facts the stereochemistry of geigerin has been partially defined.

THE sesquiterpenoid lactone, geigerin, was first isolated by Rimington and Roets[1] from *Geigeria aspera* Harv. These authors showed that geigerin, $C_{15}H_{20}O_4$, was a ketonic lactone and made a preliminary study of its chemistry. Our attention was first directed to this compound by Professor C. Rimington, F.R.S., who very kindly made available to us his original specimens. Preliminary investigations carried out in 1954 in collaboration with Dr. E. W. Warnhoff revealed that geigerin was an αβ-unsaturated derivative of *cyclo*pentanone, but the work could not be pursued to completion owing to lack of material.

In the meantime important contributions to the chemistry of geigerin have been made by Perold[2,3] who has shown, by dehydrogenation of suitable derivatives to, *inter al.*, guaiazulene (I), that the compound is a guianolide.[4] On mild treatment with alkali the lactone ring of geigerin is opened with formation of *allo*geigeric acid, $C_{15}H_{22}O_5$.[1-3] This acid is no longer an αβ-unsaturated ketone and does not relactonise spontaneously. On the basis of these and other observations Perold[3] proposed the constitution (II) for geigerin.

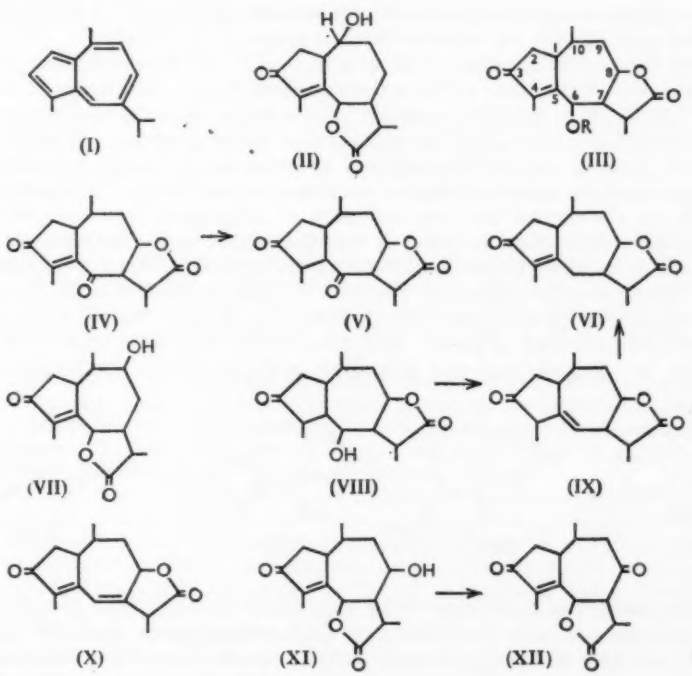
Through the generosity of Dr. G. W. Perold and of Dr. J. P. de Villiers (National Chemical Research Laboratory, C.S.I.R., South Africa), both of whom very kindly provided us with geigerin, we have been able to investigate further the interesting chemistry of this lactone. We have been able to show conclusively that geigerin is represented by formula (III; R = H).

Ozonolysis of geigerin gave acetic acid, confirming the placing of the αβ-unsaturated ketone grouping. Contrary to earlier reports,[1-3] geigerin was readily acetylated to a

* Part X, *J.*, 1958, 963.

[1] Rimington and Roets, *Onderstepoort J. Vet. Sci.*, 1936, **7**, 485.
[2] Perold, *J. S. African Chem. Inst.*, 1955, **8**, 12.
[3] Perold, *J.*, 1957, 47.
[4] See Cekan, Herout, and Šorm, *Chem. and Ind.*, 1954, 604.

monoacetate (III; R = Ac) and oxidised to dehydrogeigerin (IV). Since the latter was stable to chromic acid and since geigerin contains 3 *C*-Me groups, it follows that geigerin cannot be a primary alcohol, but must be secondary. On the basis of this and other considerations we at first favoured [5] the constitution (VII) for geigerin. This was shown to be incorrect by the following experiments. Reduction of geigerin with zinc dust and acetic acid gave in good yield a deoxygeigerin (VI). The usual mechanistic considerations [6] suggest that this ready removal of the secondary hydroxyl group requires the presence either of an α-ketol or of a vinylogous α-ketol. The properties of dehydrogeigerin (IV) (see further below) exclude the former possibility. It was still conceivable, however, that the lactone ring terminated in the vinylogous α-position and that a different lactone ring was formed by relactonisation on to the (original) secondary hydroxyl group. This was excluded by the following experiments. Geigerin was converted into its methanesulphonate (III; R = Me·SO_2) in the usual way. Treatment of this with sodium iodide [7] and reduction of the resulting iodide with zinc under mild conditions gave the same deoxygeigerin. Similarly dihydrogeigerin,[3] now represented as (VIII), gave a methanesulphonate. When this was refluxed with collidiue, the product contained deoxygeigerin, isolated as its 2 : 4-dinitrophenylhydrazone. Clearly the methanesulphonate group must be eliminated to give, at least partly, the βγ-unsaturated ketone (IX), readily isomerised to (VI).



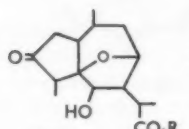
The properties of dehydrogeigerin are fully in accord with its formulation as (IV). Thus it was readily reduced by zinc dust, even at room temperature, to give dehydrodihydrogeigerin (V), a reaction characteristic of an ene-1 : 4-dione.

[5] See Barton and de Mayo, *Quart. Rev.*, 1957, **11**, 189.
[6] See Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.
[7] For example, Prelog, Norymberski, and Jeger, *Helv. Chim. Acta*, 1946, **29**, 360.

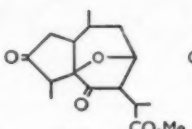
On treatment with perchloric acid in acetic acid geigerin was dehydrated to anhydrogeigerin. On the basis of its ultraviolet spectrum ($\lambda_{max.}$ 297 mμ) and infrared bands at 1759 (γ-lactone), 1685 (*cyclo*pentenone), and 1649 and 1596 cm.$^{-1}$ (conjugated ethylenic linkages) this is formulated as (X).

The infrared spectrum of geigerin [2,3] shows that it is a γ-lactone. Deoxygeigerin (VI) has infrared bands at 1762 (γ-lactone), 1693 (*cyclo*pentenone), and 1644 cm.$^{-1}$ (conjugated ethylenic linkage) and thus retains the same γ-lactone grouping. We have now obtained additional evidence in support of the placing of this γ-lactone grouping in the geigerin molecule as in (III; R = H). Treatment of geigerin methanesulphonate with base gave a mixture of two products: with aqueous sodium hydroxide at room temperature the ester afforded mainly 6-*epi*geigerin (as III; R = H), the constitution of which was shown by chromic acid oxidation to dehydrogeigerin (IV); treatment with ethanolic potassium hydroxide under similar conditions furnished, besides some 6-*epi*geigerin, a further isomeric γ-lactone, showing infrared bands at 1768 (γ-lactone), 1695 (*cyclo*pentenone), and 1637 cm.$^{-1}$ (conjugated ethylenic linkage). This must be formulated as 6-*epiallo*geigerin * (XI) because on chromic acid oxidation it gave a new diketone, dehydro-6-*epiallo*geigerin (XII). The chromophore of the latter compound was stable to zinc dust reduction in agreement with its formulation. A compound obtained earlier [9] from *neo*tenulin and formulated identically shows the same resistance (of the chromophore) to zinc dust reduction. These results, therefore, not only confirm the position of the lactone ring in geigerin but also support the earlier structural proposals for tenulin.[8]

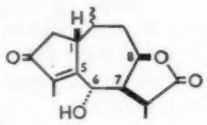
We now turn to the structure of *allo*geigeric acid.† We formulate this compound as (XIII; R = H) on the basis of the following experiments. Oxidation of methyl *allo*geigerate [3] (XIII; R = Me) with chromic acid afforded methyl dehydro*allo*geigerate (XIV). From its infrared spectrum the latter contained no hydroxyl group. If methyl dehydro-*allo*geigerate contains one methoxycarbonyl and two ketone groups it is clear that the fifth oxygen must be either ethereal or a further ketone group. The latter was made improbable by the observation that reduction of *allo*geigeric acid with zinc dust and acetic acid gave deoxygeigerin (VI). It was then found that treatment of either *allo*geigeric acid or its methyl ester with the 2 : 4-dinitrophenylhydrazine reagent furnished the 2 : 4-dinitrophenylhydrazone of geigerin. It thus seemed that the conversion of geigerin into *allo*geigeric acid must be reversible. In the event refluxing *allo*geigeric acid with acetic acid gave back geigerin. Also it was found that, from ultraviolet absorption spectra, the true geigeric acid and *allo*geigeric acid must be in equilibrium in alkaline



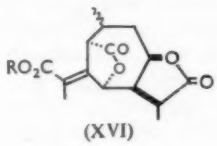
(XIII)



(XIV)



(XV)



(XVI)

solution, the position of equilibrium being approximately 90% on the side of *allo*geigeric acid. Acidification of such a mixture gave back some geigerin (from the true geigeric acid). The addition of the secondary hydroxyl, revealed by opening the lactone ring of geigerin, to the β-position of the αβ-unsaturated ketone function explains these facts in a unique manner.

* We use the prefix *allo* for this compound in the same sense as it has been employed by Braun, Herz, and Rabindran.[8]

† We gratefully acknowledge helpful discussions with Mr. S. K. Pradhan in connection with the chemistry of this compound.

[8] See Braun, Herz, and Rabindran, *J. Amer. Chem. Soc.*, 1956, **78**, 4423.
[9] Barton and de Mayo, *J.*, 1956, 142.

The properties of *allo*geigeric acid throw some light on the stereochemistry of geigerin. *allo*Geigeric acid does not lactonise, even on sublimation at 200°. The hydroxyl and the carboxyl group bearing side chain must, therefore, be *trans* to each other. Since *allo*-geigeric acid always reverts to geigerin, rather than to the isomeric (*trans*) lactone engaging the 6-hydroxyl group, it is reasonable to accept the lactone ring of geigerin as *cis*. If we place the 7-side chain in the customary β-configuration, then geigerin can be represented (at $C_{(6)}$, $C_{(7)}$, and $C_{(8)}$) as in (XV). 6-*epi*Geigerin (see above) does *not* undergo an *allo*-geigeric acid-type change with alkali. If one has the 6-, 7-, and 8-substituents all *cis* to each other, then this lack of $C_{(8)} \longrightarrow C_{(5)}$ bridging is understandable. It has also been argued from rotatory-dispersion studies [10] that the hydrogen at $C_{(1)}$ in geigerin is β (see XV).

We may now consider the dilactone-acid obtained by de Waal [11] on oxidation of geigerin with nitric acid. We formulate this substance as (XVI; R = H) on the basis of the following evidence. The ultraviolet absorption spectra of the acid and of its methyl ester (XVI; R = Me) indicated the presence of an αβ-unsaturated CO_2H (CO_2Me) function. The infrared spectrum of the acid showed bands at 1782 (γ-lactone; strength equivalent to two groups) and 1720 cm.$^{-1}$ (carboxyl). The ester gave bands at 1781 with a shoulder at 1800 (two γ-lactones), 1726 (αβ-unsaturated methoxycarbonyl), and 1670 cm.$^{-1}$ (conjugated ethylenic linkage). Ozonolysis of the acid gave acetic acid, confirming the presence of the system $CO_2H{\cdot}CMe{:}C<$. It will be seen that the formation of the additional γ-lactone ring in (XVI; R = H) is consistent with the stereochemistry summarised in the expression (XV).

Experimental

M. p.s were taken on the Kofler block. Unless specified to the contrary, $[\alpha]_D$ refer to $CHCl_3$, ultraviolet absorption spectra to EtOH, and infrared absorption spectra to $CHCl_3$ solutions. Microanalyses were carried out by Mr. J. M. L. Cameron (Glasgow) and Miss J. Cuckney (Imperial College) and their respective associates. Light petroleum refers to the fraction of b. p. 60—80°.

Geigerin and its Derivatives.—Geigerin gave 16·25% of *C*-Me (Calc. for 3 *C*-Me, 17·05%). Geigerin, left overnight with pyridine–acetic anhydride, gave *geigerin acetate* (III; R = Ac) as colourless needles (from chloroform–ether–hexane), m. p. 130—131°, $[\alpha]_D$ −102° (*c* 0·92), $\lambda_{max.}$ 237 mμ (ε 16,000), $\nu_{max.}$ 1776 (γ-lactone), 1751 (acetate), 1712 (*cyclo*pentanone) and 1658 cm.$^{-1}$ (conjugated ethylenic linkage) (Found: C, 66·85; H, 7·15. $C_{17}H_{22}O_5$ requires C, 66·65; H, 7·25%).

Geigerin (320 mg.) was left overnight with methanesulphonyl chloride (6 ml.) and pyridine (30 ml.). The neutral product was filtered in methylene dichloride solution through alumina (Grade III). Crystallisation from benzene–ether afforded geigerin methanesulphonate (III; R = Me·SO_2), m. p. 143—145°, $[\alpha]_D$ −124° (*c* 1·42), $\lambda_{max.}$ 236 mμ (ε 15,300), $\nu_{max.}$ 1770 (γ-lactone), 1703 (*cyclo*pentenone), and 1647 cm.$^{-1}$ (conjugated ethylenic linkage).

Ozonolysis of Geigerin.—Geigerin (100 mg.) in ethanol-free chloroform (40 ml.) was ozonised at room temperature until the maximum at 238 mμ had disappeared. The chloroform solution was shaken with water, left for 2 hr., and then steam-distilled until no more volatile acid was evolved. The combined distillate was neutralised with sodium hydroxide solution, concentrated *in vacuo*, and then, after adjustment of the pH to 7, treated with *p*-bromophenacyl bromide (330 mg.) in ethanol (10 ml.) in the usual way. Chromatography of the product gave *p*-bromophenacyl acetate (67 mg.), identified by m. p., mixed m. p., and infrared spectrum.

allo*Geigeric Acid* (XIII; R = H) *and its Derivatives.*—Geigerin (520 mg.) was treated at room temperature with 0·1N-ethanolic potassium hydroxide (100 ml.). After 15 hr. ε had reached 1700, and after 40 hr. 1400, unchanged on further standing. Separation into neutral and acid fractions gave geigerin (51 mg.) and *allo*geigeric acid (167 mg.) respectively. Treatment of *allo*geigeric acid with the same concentration of ethanolic potassium hydroxide gave (at equilibrium) the same value for $\varepsilon_{max.}$.

Methyl *allo*geigerate (93 mg.) was treated with excess of chromium trioxide in acetic acid

[10] Djerassi, Osiecki, and Herz, *J. Org. Chem.*, 1957, **22**, 1361.
[11] de Waal, *Onderstepoort J. Vet. Sci.*, 1938, **10**, 395.

XUM

at room temperature in the usual way. Chromatography over silica gel and sublimation of the fractions eluted with ether gave needles of *methyl dehydroallogeigerate* (XIV), m. p. 125—128°, $[\alpha]_D$ +79° (*c* 1·23), $\lambda_{max.}$ 287 mμ (ε 77), $\nu_{max.}$ 1741 and 1721 cm.$^{-1}$ (in CCl_4) (Found: C, 65·45; H, 7·25. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·55%).

Treatment of either *allo*geigeric acid or its methyl ester with methanolic hydrochloric acid containing 2 : 4-dinitrophenylhydrazine at room temperature gave, in one day, geigerin 2 : 4-dinitrophenylhydrazone identified, after chromatography over bentonite–Celite and crystallisation from chloroform–methanol, by m. p., mixed m. p., and ultraviolet and infrared spectra. *allo*-Geigeric acid (36·5 mg.) in acetic acid (14 ml.) was refluxed for 23 hr. Separation into acid and neutral fractions gave neutral material. This was chromatographed over alumina (Grade III) to furnish geigerin (15 mg.), identified by m. p., mixed m. p., and infrared spectrum.

Deoxygeigerin.—(a) *From geigerin.* Geigerin (76 mg.), zinc dust (500 mg.), and acetic acid (4·0 ml.) were refluxed for 18 hr. The neutral product (69 mg.), crystallised from ethyl acetate–hexane, gave *deoxygeigerin* (VI), m. p. (needles) 131—135°, $[\alpha]_D$ −17° (*c* 1·12), $\lambda_{max.}$ 238 mμ (ε 14,000) (Found: C, 72·65; H, 8·0. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%). The derived 2 : 4-*dinitrophenylhydrazone* crystallised from chloroform–ethanol as red needles, m. p. 271—173°, $\lambda_{max.}$ (in $CHCl_3$) 387 mμ (ε 28,900) (Found: C, 58·6; H, 5·65; N, 12·5. $C_{21}H_{24}O_6N_4$ requires C, 58·85; H, 5·65; N, 13·1%).

(b) *From geigerin methanesulphonate.* The ester (112 mg.) and anhydrous sodium iodide (1·24 g.) were refluxed in acetone (9 ml.) for 24 hr. The product was shaken with zinc dust (550 mg.) in acetic acid (5 ml.) at room temperature overnight. The resultant halogen-free oil was chromatographed over alumina (Grade III), to give deoxygeigerin (VI) (17 mg.), identified by m. p., mixed m. p., and infrared spectrum.

(c) *From* allo*geigeric acid.* The acid (48 mg.), in acetic acid (3·5 ml.), was refluxed with zinc dust (400 mg.) for 19 hr. Chromatography of the product over alumina gave deoxygeigerin (15 mg.), identified by m. p., mixed m. p., and infrared spectrum.

(d) *From dihydrogeigerin.*[3] Dihydrogeigerin (136 mg.) was left with methanesulphonyl chloride (1·5 ml.) in pyridine (13 ml.) at room temperature for 21 hr. The product was refluxed with collidine (10 ml.) for 2 hr. to give, on conversion into the 2 : 4-dinitrophenylhydrazone, the derivative of deoxygeigerin. This was identified by m. p., mixed m. p., and ultraviolet and infrared spectra.

Dehydrogeigerin.—Geigerin (300 mg.) in " AnalaR " acetic acid (30 ml.) was treated with chromium trioxide (225 mg.) in the same solvent (150 ml.). The neutral product, crystallised from benzene–hexane, gave *dehydrogeigerin* (IV) (243 mg.), m. p. (prisms) either 108° and then 132—136°, or 132—136°, $[\alpha]_D$ +3° (*c* 0·73), +5° (*c* 1·58), $\lambda_{max.}$ 234 mμ (ε 10,150) (Found: C, 68·4; H, 6·7. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%).

Dehydrodihydrogeigerin (V).—(*a*) Dehydrogeigerin (IV) (150 mg.) and zinc dust (600 mg.) were heated with acetic acid (10 ml.) at 100° for 20 hr. The neutral product (140 mg.) was crystallised from benzene, to give *dehydrodihydrogeigerin* (V), m. p. (plates) 237—238°, $[\alpha]_D$ +135° (*c* 0·89), $\lambda_{max.}$ 285 mμ (ε 80) (Found: C, 68·35; H, 7·85. $C_{15}H_{20}O_4$ requires C, 68·15; H, 7·65%).

(*b*) Dehydrogeigerin (35·4 mg.), zinc dust (200 mg.), and acetic acid (10 ml.) were shaken at room temperature for two days. Crystallisation from benzene gave the same dehydrodihydrogeigerin as described above.

Anhydrogeigerin (X).—(*a*) Geigerin (264 mg.) was heated with 72% aqueous perchloric acid (2 ml.) and " AnalaR " acetic acid (18 ml.) on the steam-bath for 8 hr., the reaction being followed by the development of an ultraviolet maximum at 297 mμ. The neutral fraction (223 mg.) was chromatographed over alumina (Grade III) to give, on elution with benzene, *anhydrogeigerin* (X). Recrystallised from ethyl acetate–hexane and then from aqueous methanol, this had m. p. 160—162°, $[\alpha]_D$ −203° (*c* 0·69), $\lambda_{max.}$ 211 and 297 mμ (ε 9000 and 16,100 respectively) (Found: C, 73·4; H, 7·35. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·35%). The derived 2 : 4-*dinitrophenylhydrazone* (dark red needles from chloroform–methanol) had m. p. 275—280°, $\lambda_{max.}$ (in $CHCl_3$) 403 mμ (ε 31,200) (Found: C, 58·9; H, 5·25; N, 13·25. $C_{21}H_{22}O_6N_4$ requires C, 59·15; H, 5·2; N, 13·15%).

(*b*) Geigerin methanesulphonate (50 mg.) and collidine (6 ml.) were refluxed for 2 hr. The product gave, on conversion into the 2 : 4-dinitrophenylhydrazone, the derivative of anhydrogeigerin mentioned above (m. p. and mixed m. p.).

Treatment of Geigerin Methanesulphonate with Alkali.—(a) *With aqueous sodium hydroxide.*

XUM

The ester (680 mg.) was shaken overnight with 0·1N-aqueous sodium hydroxide (100 ml.). Extraction of the alkaline solution with ether gave a fraction (38 mg.) which crystallised from ether, then having m. p. 180—181°. Acidification with 6N-hydrochloric acid and further extraction gave a neutral gum which was chromatographed over alumina (grade III). Elution with benzene–ether gave crystalline material, m. p. 180°, not depressed on admixture with the substance obtained from the neutral fraction (see above). Elution with ether gave material of m. p. 175°. The combined fractions were crystallised from chloroform–hexane, to give 6-epi*geigerin* (as III; R = H) (53 mg.), m. p. 177—179°, $[\alpha]_D$ −51° (*c* 1·01), $\lambda_{max.}$ 238 mμ (ε 15,100) (Found: C, 68·15; H, 7·8. $C_{15}H_{20}O_4$ requires C, 68·15; H, 7·65%). There was a marked depression in m. p. on admixture with geigerin. Elution with acetone gave a further fraction (36 mg.), m. p. 213—230° (see below).

(b) Geigerin methanesulphonate (750 mg.) was treated overnight with 0·1N-ethanolic potassium hydroxide (120 ml.). Dilution with water, acidification with 6N-hydrochloric acid, and chromatography as above gave, as the more easily eluted compound, 6-*epi*geigerin (25 mg.), identical with the lactone described above and, as the less easily eluted substance, 6-epiallo-*geigerin* (XI). Recrystallised from chloroform–ethyl acetate, this (50 mg.) had m. p. 245—248°, $[\alpha]_D$ −83° (*c* 1·32), $\lambda_{max.}$ 237 mμ (ε 15,400) (Found: C, 68·4; H, 7·75%). 6-*epiallo*Geigerin was not depressed in m. p. on admixture with the more difficult fraction to elute, m. p. 213—230°, referred to under (a) above.

Oxidation of 6-*epi*geigerin (18 mg.) with chromium trioxide as for the oxidation of geigerin (see above) gave dehydrogeigerin, identified by m. p., mixed m. p., $[\alpha]_D$, and infrared spectrum.

Oxidation of 6-*epiallo*geigerin (56 mg.) under the same conditions gave a product (52 mg.) which, on crystallisation from benzene, furnished *dehydro*-6-epiallo*geigerin* (XII), m. p. 149—153°, $[\alpha]_D$ +31° (*c* 1·12), $\lambda_{max.}$ (in dioxan) 235 mμ (ε 7700) (Found: C, 68·85; H, 7·15. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). In EtOH the ultraviolet spectrum had initially $\lambda_{max.}$ 213 and 239 mμ (ε 6400 and 7800 respectively), $\lambda_{inflex.}$ 263 and 305 mμ (ε 4600 and 1000 respectively).

Dehydro-6-*epiallo*geigerin (47 mg.) and zinc dust (100 mg.) were refluxed in acetic acid (10 ml.) for 26 hr. (spectrophotometric control). There was no reduction in $\varepsilon_{max.}$.

The Dilactone-acid (XVI; R = H) *of de Waal.*[11]—Recrystallised from ethyl acetate this acid had m. p. 278—282°, $\lambda_{max.}$ 213 mμ (ε 6300), and $\nu_{max.}$ 3190—2610 (carboxylic acid), 1782 (bis-γ-lactone), and 1720 cm.$^{-1}$ (carboxyl). The derived methyl ester (XVI; R = Me), after crystallisation from benzene–light petroleum, had m. p. 185—190°, $[\alpha]_D$ +182° (*c* 1·52), $\lambda_{max.}$ 220 mμ (ε 10,100), $\nu_{max.}$ 1800 and 1781 (γ-lactones), 1726 (methoxycarbonyl) and 1670 cm.$^{-1}$ (conjugated ethylenic linkage).

The dilactone-acid (40 mg.) in chloroform (30 ml.) was ozonised until the absorption maximum at 218 mμ had disappeared. The volatile acid produced was isolated as in the ozonolysis of geigerin (see above) and identified as acetic acid.

We thank the Government Grants Committee of the Royal Society and Imperial Chemical Industries Limited for financial assistance. One of us (J. E. D. L.) acknowledges with thanks the award of Scholarships by Le Centre National de la Recherche Scientifique (France), the British Council, and the Medical Research Council.

The University, Glasgow, W.2.
Imperial College, London, S.W.7.

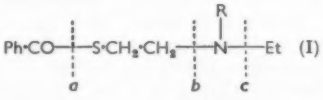
[*Received, July 28th*, 1958.]

913. *Thiol-esters. Part II.*[1] *The Chlorination of 2-Diethylaminoethyl Thiolbenzoate and the Rearrangement of 2-Alkylaminoethyl Thiolbenzoates.*

By C. J. M. Stirling.

Chlorination of 2-diethylaminoethyl thiolbenzoate causes *N*-dealkylation; the subsequent reactions have been traced in a study of the stability of a series of 2-alkylaminoethyl thiolbenzoates. These esters rearrange to benzamido-thiols which then undergo intermolecular self-benzoylation.

Crane, Forrest, Stephenson, and Waters [2] showed that aqueous chlorination of tertiary amines caused dealkylation at the nitrogen atom by successive α-chlorination and hydrolysis. *N*-Chloroamides were used to trace the systematic breakdown of the tertiary bases by successive chlorination of the alkyl groups. In the present work, 2-diethylaminoethyl thiolbenzoate (I; R = Et) reacted rapidly with an excess of aqueous chlorine in acid solution, to give a quantitative yield of benzoic acid together with *NN*-diethyltaurine. As observed previously,[2] chlorine does not attack protonated amino-groups, and with the thiol-ester carbonyl–sulphur fission occurs exclusively. In alkaline hypochlorite, reaction with the ester occurs both at the amino-group and at the sulphur atom. The products are benzoic acid, diethylamine, and acetaldehyde (together with the product of further chlorination, chloroform). These products are derived respectively from cleavages at (*a*), (*b*), and (*c*). In addition, a chloramine, which on reduction gave only neutral material, was obtained. This chloramine could not be purified but was probably the ester (I; R = Cl). Neither of the products resulting from cleavages at (*b*) and (*c*), namely, 2-(benzoylthio)ethanal and 2-ethylaminoethyl thiolbenzoate (I; R = H), was found, and no pure taurine derivative was isolated.



An attempt to obtain 2-ethylaminoethyl thiolbenzoate from 2-ethylaminoethyl chloride hydrochloride and potassium thiolbenzoate gave only a neutral compound, $C_{18}H_{19}O_2NS$. Its infrared spectrum, which was closely similar to that of the neutral material obtained from the reduction of the *N*-chloro-amine, showed carbonyl bands at 1668 and 1630 cm.$^{-1}$, the latter that of a tertiary amide, together with a strong band at 911 cm.$^{-1}$. Alkaline hydrolysis gave benzoic acid and a thiol ($C_{12}H_{15}ONS$), from whose spectrum the bands at 1668 and 911 cm.$^{-1}$ were absent. Comparison with the spectra of other thiol-esters considered in this investigation has shown that these bands are to be associated with the thiolcarboxylic group. On this evidence the original compound was considered to be *NS*-dibenzoyl-2-ethylaminoethanethiol (II; R = Et) and the thiol, therefore, to be *N*-benzoyl-2-ethylaminoethanethiol (IV; R = Et). This was confirmed by synthesis (see scheme p. 4525).

Attention was turned to anhydrous chlorination of the ester; *NN'*-dichloro-*NN'*-di-(2 : 4 : 6-trichlorophenyl)urea reacted rapidly with 2-diethylaminoethyl thiolbenzoate to give benzoyl chloride, diethylamine, *NS*-dibenzoyl-2-ethylaminoethanethiol, and 2-ethylaminoethyl thiolbenzoate hydrochloride. The last product resulted from hydrolysis of the α-chloro-amine:

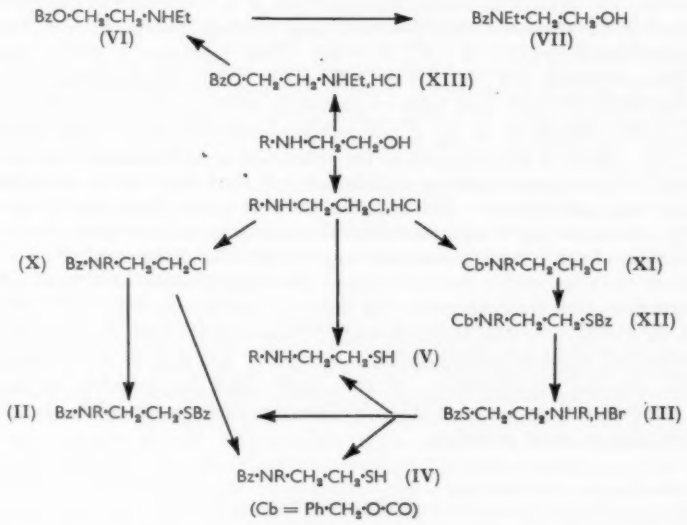
$$Ph{\cdot}CO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}NEt{\cdot}CHCl{\cdot}CH_3 \xrightarrow{H_2O} Ph{\cdot}CO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}NHEt,HCl + CH_3{\cdot}CHO$$

No free secondary amino-ester was isolated.

[1] The paper by Stirling, *J.*, 1957, 3597, is regarded as Part I.
[2] Crane, Forrest, Stephenson, and Waters, *J.*, 1946, 827.

XUM

Of the products obtained in reactions with both chlorine and the chloro-amide, only *NS*-dibenzoyl-2-ethylaminoethanethiol could not be accounted for as a product of α-chlorination of the *N*-substituent or of carbonyl–sulphur fission. This, together with the failure to isolate 2-ethylaminoethyl thiolbenzoate, prompted an investigation of the stability of 2-alkylaminoethyl thiolbenzoates. Alkylaminoalkyl carboxylic esters undergo [3,4] $O \longrightarrow N$ acyl migration to give amides, but β-amino-thiol-esters have been less investigated. Two methods [5,6] for the synthesis of 2-acylaminoethanethiols involve the assumption that an amino-thiol-ester is initially formed, but in neither instance was it isolated. Wieland and Hornig [7] have obtained ω-aminoalkyl thiolcarboxylic esters as the hydrochlorides and have measured the rates of rearrangement of the free bases without isolation of the products. In no case was formation of *NS*-diacylated compounds reported. 2-Ethylaminoethyl thiolbenzoate hydrobromide (III; R = Et) was obtained as outlined in the scheme below. Liberation of the base gave not only the expected product of $S \longrightarrow N$ migration, *N*-benzoyl-2-ethylaminoethanethiol (IV; R = Et), but also *NS*-dibenzoyl-2-ethylaminoethanethiol (II; R = Et). No basic product was obtained. Similarly, 2-aminoethyl thiolbenzoate hydrobromide (III; R = H) gave a mixture of 2-benzamidoethanethiol (IV; R = H) (cf. Kuhn and Quadbeck [5]) and *NS*-dibenzoyl-2-



aminoethanethiol (II; R = H). This showed that 2-alkylaminoethyl thiolbenzoates undergo rapid $S \longrightarrow N$ benzoyl migration which is followed by benzoylation of the resulting thiol. The formation of dibenzoylated compounds in these reactions must be accompanied by elimination of a 2-alkylaminoethanethiol (V). Attempts to isolate this thiol (R = H or Et) failed, but from 2-*cyclo*hexylaminoethyl thiolbenzoate hydrobromide (III; R = *cyclo*hexyl) all three compounds (II, IV, and V; R = *cyclo*hexyl) were obtained. Rearrangement of the thiol-esters was much faster than that of the oxygen analogue (VI) which only slowly rearranged to the amido-alcohol (VII). No corresponding *NO*-dibenzoyl compound could be isolated.

[3] Phillips and Baltzly, *J. Amer. Chem. Soc.*, 1947, **69**, 200.
[4] Cope and Hancock, *ibid.*, 1944, **66**, 1453, and references there cited.
[5] Kuhn and Quadbeck, G.P. 893,795.
[6] McQuillin and Stewart, *J.*, 1955, 2966.
[7] Wieland and Hornig, *Annalen*, 1956, **600**, 12.

In principle, the *NS*-dibenzoyl compound obtained from the thiol-ester may arise in two ways:

(i) Intermolecular aminolysis, *i.e.*, displacement of 2-alkylaminoethanethiol by attack of the secondary amino-group at the carbonyl group of the second molecule. This, however, is unlikely, as the $S \longrightarrow N$ migration is rapid whereas aminolysis of thiol-esters is slow. 2-Diethylaminoethyl thiolbenzoate and di-*n*-butylamine, for example, required 1 hr. at 170° for 20% reaction.

(ii) Transesterification. Reaction of the amido-thiol (IV), the product of rearrangement, with free amino-ester would account for the formation of the *NS*-dibenzoyl compounds. Transesterification of thiol-esters has been reported [8] and, to test this possibility, 2-ethylaminoethyl thiolbenzoate was liberated from the hydrobromide in the presence of *N*-*p*-chlorobenzoyl-2-ethylaminoethanethiol (VIII). The higher-boiling fraction contain-

$Cl{\cdot}C_6H_4{\cdot}CO{\cdot}NEt{\cdot}CH_2{\cdot}CH_2{\cdot}SH$ (VIII)

$R{\cdot}C_6H_4{\cdot}CO{\cdot}NEt{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CO{\cdot}C_6H_4R'$ (IX)

ing *NS*-dibenzoyl compounds was found to contain chlorine, showing that the substituted thiol had reacted. The infrared spectrum of this fraction, however, contained a band at 719 cm.$^{-1}$ which was present in neither the spectrum of *NS*-dibenzoyl-2-ethylaminoethanethiol nor that of the expected chlorine-containing product, *S*-benzoyl-*N*-*p*-chlorobenzoyl-2-ethylaminoethanethiol (IX; R = Cl, R′ = H). This band was, however, present in the spectra of the compounds (IX; R = H or Cl, R′ = Cl). This suggested that the substituted thiol had reacted with itself, and later examination of the residue from the distillation of this thiol (VIII) showed it to be *NS*-di-*p*-chlorobenzoyl-2-ethylaminoethanethiol (IX; R = R′ = Cl). Tests of the stability of the other amido-thiols considered above showed that *S*-benzoylation occurred during distillation and that therefore postulation of transesterification was unnecessary. The reaction must involve displacement of amino-thiol (V) from the amido-thiol (IV) and resembles the high-temperature alcoholysis of amides [9] and the reaction of thiols with thioamides to give esters of dithio-acids.[10]

In spite of the observation that *NS*-dibenzoyl-2-alkylaminoethanethiols arise directly from 2-alkylaminoethyl thiolbenzoates, the failure to isolate the thiol (IV; R = Et) from the partial chlorination of 2-diethylaminoethyl thiolbenzoate suggests that the formation of *NS*-dibenzoyl-2-ethylaminoethanethiol is probably not due to the decomposition of amido-thiol. Instead, benzoylation of the amido-thiol (or possibly of unrearranged secondary amino-ester) by benzoyl chloride simultaneously produced in the chlorination, must be regarded as more probable.

Experimental

Extracts were dried over $MgSO_4$. The light petroleum used had b. p. 40—60° unless otherwise stated. *NN*′-Dichloro-*NN*′-di-(2 : 4 : 6-trichlorophenyl)urea [11] had m. p. 175° (decomp.) (Found: Available chlorine, 14·7. Calc. for $C_{13}H_4ON_2Cl_8$: 14·6%).

2-Diethylaminoethyl Thiolbenzoate.—Potassium thiolbenzoate (41 g.) and 2-diethylaminoethyl chloride hydrochloride (48 g.) in water (200 ml.) were kept at 100° for 1 hr. The solution was basified with sodium hydroxide and extraction with chloroform gave the ester (60 g.), b. p. 112°/0·1 mm., n_D^{25} 1·5465 (Found: C, 65·5; H, 8·3. Calc. for $C_{13}H_{19}ONS$: C, 65·8; H, 8·0%). The hydrochloride had m. p. 139—140° (Found: N, 5·1. Calc. for $C_{13}H_{20}ONClS$: N, 5·0%). Clinton, Salvador, and Laskowski [12] give m. p. 137—138·5°.

[8] Sasin, Schaeffer, and Sasin, *J. Org. Chem.*, 1957, **22**, 1183.
[9] Taylor and Baker, "Sidgwick's Organic Chemistry of Nitrogen," Oxford University Press, 1937, p. 145.
[10] Reid, Orig. Comm. 8th Internat Congr. Appl. Chem. (Appendix), Vol. 25, p. 423; *Chem. Abs.*, 1913, **7**, 2190.
[11] Chattaway and Orton, *Ber.*, 1901, **34**, 1073.
[12] Clinton, Salvador, and Laskowski, *J. Amer. Chem. Soc.*, 1949, **71**, 3366.

XUM

NN-Diethyltaurine.—The following method is superior to James's.[13] Sodium 2-bromoethanesulphonate [14] (10 g.), diethylamine (50 g.), and water (50 ml.) were heated at 150° (autoclave) for 1 hr. The mixture was evaporated to dryness and a solution of the residue (13 g.), in ethanol (50 ml.), was saturated with hydrogen chloride. Sodium chloride was centrifuged off and the mother-liquors gave the amino-acid (6 g.), m. p. 161—162° (Found: N, 7·6. Calc. for $C_6H_{15}O_3NS$: N, 7·7%).

Aqueous Chlorination of 2-Diethylaminoethyl Thiolbenzoate.—(a) *In acid.* A solution of the ester (5 g.) in 0·1N-hydrochloric acid (200 ml.) was saturated with chlorine. After removal of excess of chlorine in air, the solution was saturated with sodium chloride and extracted with methylene chloride. Evaporation of the dried extracts gave benzoic acid (2·5 g.), m. p. and mixed m. p. 121°. The aqueous solution was basified with sodium hydroxide and extracted with chloroform. Evaporation of the extracts gave no residue. The aqueous solution was then acidified, neutralised with sodium carbonate, and evaporated to dryness. The residue was extracted with hot absolute ethanol, and the extracts were saturated with hydrogen chloride and filtered. Evaporation of the filtrates gave *NN*-diethyltaurine (3 g.), m. p. and mixed m. p. 158—162°.

(b) *In alkali.* The ester (20 g.) was vigorously stirred with saturated aqueous sodium hydrogen carbonate (180 ml.), and a solution of sodium hypochlorite (8·7% available chlorine; 140 ml.; 2 atom-equivs.). When the aqueous layer gave no starch–iodide reaction the layers were separated.

The aqueous layer was acidified and extraction with ether gave benzoic acid (1·4 g.), m. p. and mixed m. p. 119—120°. The aqueous extracts, which gave a strong positive potassium hydroxide–pyridine test for chloroform, were distilled under reduced pressure. Acetaldehyde was obtained from a portion of the distillate as the 2 : 4-dinitrophenylhydrazone which, after chromatography on alumina, had m. p. and mixed m. p. 167°. No other carbonyl compound was detected. The residual aqueous solution, which did not give a derivative on treatment with aqueous 2 : 4-dinitrophenylhydrazine hydrochloride, was basified with sodium hydroxide and extracted with chloroform. The extracts, after being saturated with hydrogen chloride, were evaporated and treatment of the crystalline residue with toluene-*p*-sulphonyl chloride and aqueous sodium hydroxide gave *NN*-diethyltoluene-*p*-sulphonamide, m. p. and mixed m. p. 60—61°. The aqueous extracts were treated as described above for the isolation of taurine derivatives but no pure material was obtained.

The oil was washed with ice-cold 2N-hydrochloric acid. The washings were basified with sodium hydroxide and extracted with chloroform. Evaporation of the extracts and treatment of an ethereal solution of the residue with hydrogen chloride gave recovered ester hydrochloride (10·8 g.), m. p. and mixed m. p. 139—140°. The remainder of the oil was treated with an excess of potassium iodide and sodium thiosulphate in aqueous acetic acid. After 30 min. the solution was basified with sodium hydroxide and extracted with chloroform. Evaporation of the extracts gave a small neutral residue which did not give a 2 : 4-dinitrophenylhydrazone. The nitroprusside test was negative until the material had been treated with hot alcoholic sodium hydroxide. Attempts to obtain sufficient of the compound for purification failed but the infrared spectrum was closely similar to that of *NS*-dibenzoyl-2-ethylaminoethanethiol (below).

Reaction of Potassium Thiolbenzoate with 2-Ethylaminoethyl Chloride Hydrochloride.—2-Ethylaminoethyl chloride hydrochloride [15] (16 g.) and potassium thiolbenzoate (19·6 g.) were heated in water (100 ml.) at 95°. After 15 min. an oil separated and hydrogen sulphide was evolved. After 1½ hr. the solution was extracted with ether, and the extracts were washed with hydrochloric acid. No basic product was obtained. Evaporation of the ethereal solution and distillation of the residue gave NS-*dibenzoyl-2-ethylaminoethanethiol* (13·5 g.), b. p. 200°/0·2 mm., n_D^{25} 1·5961 (Found: C, 68·3; H, 6·3. $C_{18}H_{19}O_2NS$ requires C, 69·0; H, 6·1%). Hydrolysis (of 4·7 g.) with sodium hydroxide in aqueous acetone gave: (i) benzoic acid (1·7 g.), m. p. and mixed m. p. 119—121°; and (ii) slightly impure N-*benzoyl-2-ethylaminoethanethiol* (1·8 g.), b. p. 133°/0·1 mm., n_D^{25} 1·5612 (Found: C, 62·3; H, 7·6. $C_{11}H_{13}ONS$ requires C, 63·1; H, 7·2%). The infrared spectra of the compounds were identical with those of authentic specimens (below). Starting material (0·6 g.) was recovered from the hydrolysis.

[13] James, *J.*, 1885, **47**, 367.
[14] Marvel and Sparberg, *Org. Synth.*, 1930, **10**, 96.
[15] Lasselle and Sundet, *J. Amer. Chem. Soc.*, 1941, **63**, 2374.

XUM

N-Benzoyl-2-ethylaminoethyl Chloride (X; R = Et).—2-Ethylaminoethyl chloride hydrochloride (5 g.) was treated with benzoyl chloride (4 ml.) and 5% aqueous sodium hydroxide (50 ml.). Extraction of the product with ether and subsequent distillation gave the *chloride* (5 g.), b. p. 115°/0·2 mm., n_D^{25} 1·5395 (Found: C, 62·0; H, 6·8. $C_{11}H_{14}ONCl$ requires C, 62·4; H, 6·6%).

NS-Dibenzoyl-2-ethylaminoethanethiol (II; R = Et).—The chloride (5·7 g.) and potassium thiolbenzoate (4·8 g.) were heated under reflux in ethanol (30 ml.) for 1½ hr. Water (250 ml.) was added and the product was extracted with ether. Distillation gave the ester (6·9 g.), b. p. 220°/0·3 mm., n_D^{25} 1·5965, m. p. 49—50° (Found: C, 69·1; H, 6·4%).

S-{N-Benzoyl-2-ethylaminoethyl}thiuronium Hydrochloride.—The *salt* (16 g.), from thiourea (6·4 g.) and *N*-benzoyl-2-ethylaminoethyl chloride (20 g.), had m. p. 145° (from acetone–ethanol) (Found: Cl, 12·3. $C_{12}H_{18}ON_3ClS$ requires Cl, 12·3%).

N-Benzoyl-2-ethylaminoethanethiol (IV; R = Et).—Hydrolysis of the thiuronium salt (11 g.) with 5% aqueous sodium hydroxide and extraction of the product with chloroform, gave the thiol (6·2 g.), b. p. 125°/0·04 mm., n_D^{25} 1·5606 (Found: C, 63·0; H, 7·4%).

Anhydrous Chlorination of 2-Diethylaminoethyl Thiolbenzoate.—The ester (20 g.) was added to a solution of the octachlorodiphenylurea (40 g.) in anhydrous (P_2O_5) ethanol-free ($CaCl_2$) chloroform (300 ml.). After 15 hr. the precipitate of hexachlorodiphenylurea (31·3 g.), m. p. 316°,[11] was filtered off. Solvent was removed from the filtrate and addition of anhydrous ether (250 ml.) to the residue precipitated 2-diethylaminoethyl thiolbenzoate hydrochloride which, after being washed with acetone, had m. p. 130—133° (11 g.). The ethereal solution, after extraction with 2N-hydrochloric acid and 10% aqueous sodium carbonate, was washed with water and dried. While being dried, the ethereal solution gave a further precipitate (1·4 g.), m. p. 163° raised to 165° on crystallisation from acetone–ethanol. The infrared spectrum of the compound was closely similar to that of 2-ethylaminoethyl thiolbenzoate hydrobromide (below) and analysis showed it to be *2-ethylaminoethyl thiolbenzoate hydrochloride* (Found: C, 54·1; H, 6·7. $C_{11}H_{14}ONClS$ requires C, 53·8; H, 6·6%). Treatment of a saturated aqueous solution with saturated aqueous potassium bromide precipitated the *hydrobromide*, m. p. 169—170° (from acetone–ethanol) both alone and mixed with an authentic specimen (below). The residual ethereal solution was evaporated and the residue was fractionally distilled, giving: (i) benzoyl chloride (0·6 g.), b. p. 65°/14 mm., n_D^{25} 1·4923 (benzanilide, m. p. and mixed m. p. 161—162°); (ii) (0·4 g.), b. p. 80—140°/0·1 mm., which was not identified but whose spectrum did not contain bands at 1630 or 2500 $cm.^{-1}$ and was therefore not the amido-thiol (IV; R = Et); and (iii) *NS*-dibenzoyl-2-ethylaminoethanethiol (2·8 g.), b. p. 200°/0·2 mm., n_D^{25} 1·5967 (the spectrum was the same as that of an authentic specimen).

The aqueous alkaline extracts yielded only a trace of dark material. The acid extracts were basified with sodium hydroxide and extracted with chloroform. The dried extracts were distilled, diethylamine being isolated from the distillates as previously described, and saturation of an ethereal solution of the residue with hydrogen chloride precipitated recovered ester hydrochloride (0·4 g.,) m. p. and mixed m. p. 136°.

Reactions of 2-Alkylaminoethyl Thiolbenzoates. (a) *Series* R = Et (*see scheme*).—(a) *N-Benzyloxycarbonyl-2-ethylaminoethyl chloride* (XI). 2-Ethylaminoethyl chloride hydrochloride (15 g.) was treated with benzyl chloroformate (15 g.) and 5% aqueous sodium hydroxide (150 ml.). Extraction of the product with ether gave the *chloride* (19 g.), b. p. 112°/0·05 mm., n_D^{25} 1·5157 (Found: C, 59·8; H, 7·0. $C_{12}H_{16}O_2NCl$ requires C, 59·6; H, 6·6%).

N-Benzyloxycarbonyl-2-ethylaminoethyl thiolbenzoate (XII). The preceding chloride (16 g.) and potassium thiolbenzoate (11 g.), in ethanol (50 ml.), were heated under reflux for 3 hr. Water (200 ml.) was added and extraction of the product with chloroform gave the *ester* (10·5 g.), b. p. 200°/0·05 mm., n_D^{25} 1·5760 (Found: C, 66·0; H, 6·3. $C_{19}H_{21}O_3NS$ requires C, 66·5; H, 6·1%).

2-Ethylaminoethyl thiolbenzoate hydrobromide (III). The ester (10 g.), in dry acetic acid (10 ml.), was treated with 20% w/w hydrobromic–acetic acid (25 g.). After 1 hr. addition of anhydrous ether (200 ml.) precipitated the *ester hydrobromide* (8·3 g.), m. p. 169—170° (Found: C, 45·5; H, 5·8; Br, 27·6. $C_{11}H_{16}ONBrS$ requires C, 45·5; H, 5·5 Br, 27·5%).

Rearrangement of 2-ethylaminoethyl thiolbenzoate. The hydrobromide (8 g.), in oxygen-free water (200 ml.), was treated with sodium hydroxide (2·2 g.). The mixture was extracted with chloroform and then acidified and re-extracted. Distillation of the extracts gave: (i) *N*-benzoyl-2-ethylaminoethanethiol (3·5 g.), b. p. 132°/0·1 mm., n_D^{25} 1·5605; and (ii) *NS*-dibenzoyl-2-ethylaminoethanethiol (1·5 g.), b. p. 196°/0·1 mm., n_D^{25} 1·5493, m. p. and mixed m. p. 46—47°.

XUM

(b) *Series* R = H.—(Except where otherwise stated, the methods in this and the following series, R = *cyclo*hexyl, were the same as in the series R = Et. Yields at each stage are based on the preceding compound).

S-2-*Benzamidoethylthiuronium hydrochloride*. The *salt* (80%) (from 2-chloroethylbenzamide [16]) had m. p. 175° (from ethanol–acetone) (Found: Cl, 13·6. $C_{10}H_{14}ON_2ClS$ requires Cl, 13·7%).

2-*Benzamidoethanethiol* (IV). The product (88%) had m. p. 70° (from benzene–light petroleum). Kuhn and Quadbeck [5] give m. p. 71°.

2-*Benzamidoethyl thiolbenzoate* (II). Benzoylation (Schotten–Baumann) of the thiol gave the *ester*, m. p. 96—97° (from benzene–light petroleum) (Found: C, 67·3 H, 5·5. $C_{16}H_{15}O_2NS$ requires C, 67·3; H, 5·3%).

2-N-*Benzyloxycarbonylaminoethyl thiolbenzoate* (XII). The *ester* (82%) (from 2-*N*-benzyloxycarbonylaminoethyl bromide [17]) had m. p. 77° (from chloroform–light petroleum) (Found: C, 64·8; H, 5·7. $C_{17}H_{17}O_3NS$ requires C, 64·8; H, 5·4%).

2-*Aminoethyl thiolbenzoate hydrobromide* (III). The *salt* (76%) had m. p. 192—193° (from acetone–ethanol) (Found: C, 41·3; H, 4·8. $C_9H_{12}ONBrS$ requires C, 41·2; H, 4·6%).

Rearrangement of 2-aminoethyl thiolbenzoate. The hydrobromide (9 g.) gave: (i) 2-benzamidoethanethiol (4·6 g.), b. p. 138°/0·05 mm., m. p. and mixed m. p. 68·5—70°; and (ii) 2-benzamidoethyl thiolbenzoate (1·0 g.), b. p. 200°/0·05 mm., m. p. and mixed m. p. 90—91°.

(c) *Series* R = *cyclo*Hexyl.—N-*Benzyloxycarbonyl*-2-cyclo*hexylaminoethyl chloride* (XI). The *chloride* (63%) (from 2-*cyclo*hexylaminoethyl chloride hydrochloride [18, 19]) had m. p. 53—54° (from light petroleum) (Found: C, 64·6; H, 7·6. $C_{16}H_{22}O_2NCl$ requires C, 65·0; H, 7·5%)

N-*Benzyloxycarbonyl*-2-cyclo*hexylaminoethyl thiolbenzoate* (XII). The chloride (25 g.), potassium thiolbenzoate (20 g.), and potassium iodide (2 g.), heated in boiling ethanol for 3 hr., gave the *ester* (8·2 g.), b. p. 200°/0·05 mm., n_D^{25} 1·5749 (Found: C, 69·6; H, 7·1. $C_{23}H_{27}O_3NS$ requires C, 69·5; H, 6·9%).

2-cyclo*Hexylaminoethyl thiolbenzoate hydrobromide* (III). The *salt* (98%) had m. p. 206—207° (from ethanol) (Found: C, 52·2; H, 6·6. $C_{15}H_{22}ONBrS$ requires C, 52·3; H, 6·4%).

S-2-cyclo*Hexylaminoethylthiuronium hydrochloride*. 2-*cyclo*Hexylaminoethyl chloride hydrochloride (10 g.) and thiourea (3·8 g.) gave the *salt* (7 g.), m. p. 245° (from methanol) (Found: Cl, 25·7. $C_9H_{20}N_3ClS$ requires Cl, 25·9%).

2-cyclo*Hexylaminoethanethiol* (V). Hydrolysis of the salt (5 g.) gave the *thiol* (1·4 g.), b. p. 112°/14 mm., n_D^{25} 1·5045 (Found: C, 60·4; H, 11·0. $C_8H_{17}NS$ requires C, 60·3; H, 10·8%). The *urea thiolcarbamate*, obtained with α-naphthyl *iso*cyanate, had m. p. 207—208° (from chloroform–light petroleum) (Found: N, 8·2. $C_{30}H_{31}O_2N_3S$ requires N, 8·4%).

N-*Benzoyl*-2-cyclo*hexylaminoethyl chloride* (X). The *chloride* (55%) (from 2-*cyclo*hexylaminoethyl chloride hydrochloride) had b. p. 145°/0·05 mm., n_D^{25} 1·5437 (Found: C, 67·9; H, 8·0. $C_{15}H_{20}ONCl$ requires C, 67·8; H, 7·6%).

S-(N-*Benzoyl*-2-cyclo*hexylaminoethyl*)*thiuronium hydrochloride*. The *salt* (96%) had m. p. 207° (from acetone–ethanol) (Found: Cl, 10·3. $C_{16}H_{24}ONClS$ requires Cl, 10·4%).

N-*Benzoyl*-2-cyclo*hexylaminoethanethiol* (IV). Pure thiol could not be obtained from the hydrolysis of the thiuronium salt but treatment of the product, b. p. 148°/0·05 mm., with α-naphthyl *iso*cyanate gave the thiolcarbamate, m. p. 180° (from benzene–light petroleum) (Found: C, 72·5; H, 6·7. $C_{26}H_{28}O_3N_2S$ requires C, 72·2; H, 6·5%).

NS-*Dibenzoyl*-2-cyclo*hexylaminoethanethiol* (II). Benzoylation (Schotten–Baumann) of the crude thiol gave the *ester*, m. p. 100° (from benzene–light petroleum) (Found: C, 71·8; H, 7·1. $C_{23}H_{25}O_2NS$ requires C, 71·9; H, 6·9%).

Rearrangement of 2-cyclo*Hexylaminoethyl thiolbenzoate*. Distillation of the products gave fractions: (i) b. p. 40—50°/0·05 mm., which on treatment with α-naphthyl *iso*cyanate gave a derivative, m. p. 205—206° alone or mixed with that obtained from 2-*cyclo*hexylaminoethanethiol; and (ii) b. p. 145°/0·05 mm., which with α-naphthyl *iso*cyanate gave a derivative, m. p. 178—179° alone or mixed with that obtained from *N*-benzoyl-2-*cyclo*hexylaminoethanethiol. The residue, after crystallisation from ethanol, had m. p. 96° alone or mixed with *NS*-dibenzoyl-2-*cyclo*hexylaminoethanethiol.

[16] Fry, *J. Org. Chem.*, 1949, **14**, 887.
[17] Katchalski and Ben-Ishai, *ibid.*, 1950, **15**, 1067.
[18] Wedekind and Bruch, *Annalen*, 1929, **471**, 73.
[19] Cheney, Smith, and Binkley, *J. Amer. Chem. Soc.*, 1949, **71**, 60.

2-Ethylaminoethyl Benzoate Hydrochloride (XIII).—2-Ethylaminoethanol hydrochloride [18] was heated with benzoyl chloride at 100° until no further hydrogen chloride was evolved. Addition of ether precipitated the *salt*, m. p. 164—165° (Found: C, 57·4; H, 7·4; Cl, 15·4. $C_{11}H_{16}O_2NCl$ requires C, 57·5; H, 7·0; Cl, 15·4%).

Rearrangement of the Amino-ester.—The preceding hydrochloride (5 g.) was treated as before and distillation of the products gave fractions: (i) (1·9 g.) *2-ethylaminoethyl benzoate*, b. p. 87°/0·05 mm., n_D^{25} 1·5109 (Found: N, 7·4. $C_{11}H_{15}O_2N$ requires N, 7·3%); (ii) (1·8 g.) *N-benzoyl-2-ethylaminoethanol*, b. p. 138°/0·05 mm., n_D^{25} 1·5428 (Found: N, 7·4%). Fraction (i) with ethereal hydrogen chloride gave the ester hydrochloride, m. p. and mixed m. p. 164°, and with α-naphthyl *iso*cyanate gave the *α-naphthylurea*, m. p. 115—116° (from benzene–light petroleum) (Found: N, 7·8. $C_{22}H_{22}O_3N_2$ requires N, 7·7%). The infrared spectrum showed a C:O band at 1715 cm.$^{-1}$. Fraction (ii) was neutral, showed C:O 1611 cm.$^{-1}$, and with α-naphthyl *iso*cyanate gave the *α-naphthylcarbamate*, m. p. 102° (from benzene–light petroleum) (Found: N, 7·7%). The refractive index and infrared spectrum of the amino-ester (i) slowly changed to that of the amido-alcohol (ii).

Test of Aminolysis.—2-Diethylaminoethyl thiolbenzoate (5 g.) and di-*n*-butylamine (10 g.) were heated at 170° for 1 hr. The neutral product (0·7 g.), b. p. 122°/0·3 mm., had a C:O band at 1620 cm.$^{-1}$.

N-p-*Chlorobenzoyl-2-ethylaminoethyl Chloride.*—The *chloride* (59%) (from *p*-chlorobenzoyl chloride and 2-ethylaminoethyl chloride) had b. p. 140°/0·05 mm., n_D^{25} 1·5504 (Found: C, 53·7; H, 5·6. $C_{11}H_{13}ONCl_2$ requires C, 53·7; H, 5·3%).

S-(N-p-*Chlorobenzoyl*-2-*ethylaminoethyl*)*thiuronium Hydrochloride.*—The chloride with thiourea gave the *salt* (92%), m. p. 200—201° (from ethanol) (Found: C, 44·5; H, 5·7; N, 12·5. $C_{12}H_{17}ON_3Cl_2S$ requires C, 44·7; H, 5·3; N, 13·0%).

N-p-*Chlorobenzoyl-2-ethylaminoethanethiol* (VIII).—The salt (21 g.) was hydrolysed with 5% aqueous sodium hydroxide (200 ml.). Extraction of the product with chloroform and subsequent distillation gave the *thiol* (4·7 g.), b. p. 154°/0·1 mm., n_D^{25} 1·5708 (Found: C, 54·2; H, 6·2. $C_{11}H_{14}ONClS$ requires C, 54·2; H, 5·8%). The residue, m. p. 83—84°, after crystallisation from benzene–light petroleum (b. p. 80—100°), had m. p. 88—89° alone or mixed with an authentic specimen of NS-*di*-p-*chlorobenzoyl-2-ethylaminoethanethiol* (IX; R = R′ = Cl) (below).

Reaction of 2-Ethylaminoethyl Thiolbenzoate with N-p-Chlorobenzoyl-2-ethylaminoethanethiol.—The ester hydrobromide (8 g.) was treated with a solution of the thiol (3·6 g.) in 3% aqueous sodium hydroxide (100 ml.). Distillation of the chloroform extracts gave fractions: (i) (4·3 g.), b. p. 130—180°/0·15 mm., n_D^{25} 1·5634 (Found: Cl, 3·7%); and (ii) (3·3 g.), b. p. 206—218°/0·15 mm., n_D^{25} 1·5997 (Found: Cl, 8·5%). The infrared spectra of the two fractions have been referred to above.

S-*Benzoyl*-N-p-*chlorobenzoyl-2-ethylaminoethanethiol* (IX; R = Cl, R′ = H).—The *ester* (70%) (from *N-p*-chlorobenzoyl-2-ethylaminoethyl chloride and potassium thiolbenzoate) had b. p. 206—208°/0·08 mm., n_D^{25} 1·6006 (Found: C, 62·0; H, 5·5; Cl, 9·9. $C_{18}H_{18}O_2NClS$ requires C, 62·2; H, 5·2; Cl, 10·2%).

N-*Benzoyl*-S-p-*chlorobenzoyl-2-ethylaminoethanethiol* (IX; R = H, R′ = Cl).—Treatment of the thiol (IV; R = Et) with *p*-chlorobenzoyl chloride in pyridine gave the *ester*, b. p. 196°/0·02 mm., m. p. 63—64° (from benzene–light petroleum) (Found: C, 61·6; H, 5·3%).

NS-*Di*-p-*chlorobenzoyl-2-ethylaminoethanethiol* (IX; R = R′ = Cl).—Treatment of the thiol (VIII) with *p*-chlorobenzoyl chloride in pyridine gave the *ester*, m. p. 88—89° (from benzene–light petroleum) (Found: C, 56·5; H, 4·8. $C_{18}H_{17}O_2NCl_2S$ requires C, 56·6; H, 4·5%).

Self-benzoylation of Amido-thiols (IV).—In view of the observation that *N-p*-chlorobenzoyl-2-ethylaminoethanethiol underwent thermal self-benzoylation, the thermal stability of the other amido-thiols that have been considered in this investigation was tested. In each case, prolonged heating of the thiol at 140° gave the *NS*-dibenzoyl compound, and in the case of the *N-cyclo*hexyl compound, the amino-thiol (V) was also isolated.

The author is grateful to Professor E. L. Hirst, F.R.S., for his interest and encouragement, and the University of Edinburgh is thanked for the award of an I.C.I. Fellowship.

Department of Chemistry, University of Edinburgh. [*Received, August 1st*, 1958.]

914. *Intramolecular Aminolysis of Amides.*

By C. J. M. Stirling.

Reactions of amino-amides have been investigated with respect to (1) $N \longrightarrow N'$ acyl migration and (2) the formation of cyclic lactams.

N-Benzoyl-*N*-phenylethylenediamine (V; R = Ph) rearranges rapidly to *N*-benzoyl-*N'*-phenylethylenediamine (VI; R = Ph); when R = *cyclo*hexyl, the conversion is very slow but irreversible. *NN*-Dibenzoylethylenediamines (XIV; R = Ph or *cyclo*hexyl) rearrange very rapidly to *NN'*-dibenzoylethylenediamines (XV), but *N*-2-aminoethylphthalimide did not rearrange: instead, ethylenediamine and an unidentified acid were obtained.

4-Alkylaminobutyranilides (XVIII; R = Ph·CH_2 or *cyclo*hexyl) eliminated aniline when heated, with formation of *N*-alkylpyrrolid-2-ones (XIX), cyclisation of the benzyl compound being considerably the faster.

Reactivities of amines in the intermolecular aminolysis of amides have been measured by Smith and Adkins.[1] The observed order of reactivity was straight-chain primary > branched-chain primary ≈ secondary ⩾ aromatic. Their results agree well with more recent determinations of the nucleophilic reactivities of amines in carbonyl substitution, in particular the aminolysis of esters.[2] Intramolecular aminolysis of amides must involve either (1) rearrangement, with $N \longrightarrow N'$ acyl migration, or (2) elimination of amine, as in the intermolecular reaction, with formation of a cyclic lactam.[3,4]

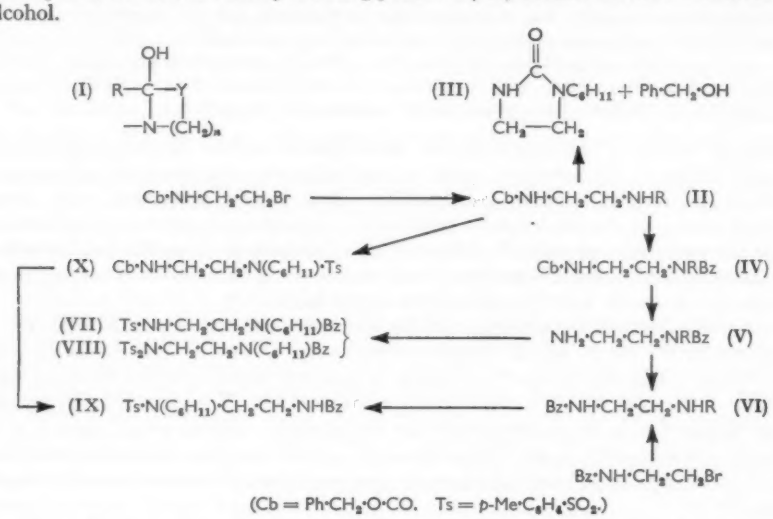
Rearrangement.—This is the counterpart of the intramolecular aminolyses of carboxylic [5] and thiolcarboxylic [6,7] esters which involve respectively, $O \longrightarrow N$ and $S \longrightarrow N$ acyl migration. These migrations occur [5] by attack of the uncharged ω-amino-group at the carbonyl group of the ester with the cyclic transition state [5,6] (I; Y = O or S). Migration occurs most rapidly,[6] as in other intramolecular nucleophilic substitutions,[8] when $n = 2$ or 3. The only instances of $N \longrightarrow N'$ migrations (Y = NH) are those of the isomerisation of *N*-acetyl-*N*-phenylthiourea [9] and certain rearrangements which do not involve uncharged amino-groups.[10]

In the present work with *N*-benzoylethylenediamines (V; R = Ph or C_6H_{11}), it has been found, as expected, that the direction and speed of migration is determined by the relative nucleophilicities of the two nitrogen atoms concerned. *N*-Benzoylethylenediamines (V; R = Ph or C_6H_{11}) have been obtained (see scheme) as their hydrobromides by benzoylation of the urethanes (II) and subsequent removal of the benzyloxycarbonyl group with hydrogen bromide.[11] On liberation of the base (V; R = Ph) rearrangement occurred rapidly and only the secondary amide (VI; R = Ph) was isolated. The *cyclo*hexyl analogue (V; R = C_6H_{11}) was more stable and treatment of the liberated base with toluene-*p*-sulphonyl chloride gave only the primary mono- and di-toluene-*p*-sulphonamides (VII and VIII respectively) in 80% yield from the urethane (IV). The infrared spectrum of the base showed that the isomer (VI) could only be present in very small quantity if at all. Rearrangement of the base, however, occurred at 150°, 56% of the urethane (IV) being accounted for as the monosulphonamide (IX) of the secondary base and 8% as the

[1] Smith and Adkins, *J. Amer. Chem. Soc.*, 1938, **60**, 657.
[2] Arnett, Miller, and Day, *ibid.*, 1950, **72**, 5635.
[3] Barrass and Elmore, *J.*, 1957, 4830.
[4] Holley and Holley, *J. Amer. Chem. Soc.*, 1952, **74**, 3069.
[5] Phillips and Baltzly, *ibid.*, 1947, **69**, 200.
[6] Wieland and Hornig, *Annalen*, 1956, **600**, 12.
[7] Stirling, preceding paper.
[8] Newman, "Steric Effects in Organic Chemistry," Wiley, New York, 1956.
[9] Wheeler, *Amer. Chem. J.*, 1902, **27**, 270.
[10] Houben-Weyl, "Methoden der Organischen Chemie," Thieme, Stuttgart, 1957, Vol. XI, Part 1, p. 939.
[11] Ben-Ishai and Berger, *J. Org. Chem.*, 1952, **17**, 1564.

XUM

disulphonamide (VIII) of the primary base. The structure of the sulphonamide (VII) was confirmed by conversion into the disulphonamide, and that of the isomer (IX) by its formation from the sulphonamido-urethane (X). Isolation of both isomers under these conditions suggested that they existed in equilibrium. This possibility was tested by examination of the product of the reaction of *N*-2-bromoethylbenzamide with *cyclo*hexylamine. The infrared spectrum of the product (twice distilled at 167°) and of its toluene-*p*-sulphonamide showed that no primary amine was obtained. The isomeric benzamides (V and VI; R = C_6H_{11}) are not, therefore, in equilibrium although conversion of (V) into (VI) is extremely slow. In this connection, the urethane (II; R = C_6H_{11}) was stable, but at 180° cyclisation to the tetrahydro-oxoglyoxaline (III) occurred with elimination of benzyl alcohol.



(Cb = Ph·CH_2·O·CO. Ts = *p*-Me·C_6H_4·SO_2·)

These results are in accord with reactivities observed in intermolecular reactions [1,2] and the conversion of the amide (V) into its isomer (VI; R = C_6H_{11}) reflects the lowering of nucleophilic reactivity caused by α-branching.

The ready acylation of amines by *N*-acylamides [12] suggested that intramolecular aminolysis of such compounds should be fast. The *NN*-dibenzoyl-*N'*-benzyloxycarbonylethylenediamines (XII; R = Ph or C_6H_{11}) were obtained (see scheme) by treatment of the *N*-benzoylethylenediamines with benzyl chloroformate and subsequent benzoylation of the urethanes (XI) at the amido-nitrogen atom.[13] Removal of the benzyloxycarbonyl group then gave the *NN*-dibenzoylethylenediamines as the hydrobromides (XIII). In each case, and in spite of the low nucleophilicity of the aromatic amine (R = Ph), very rapid benzoyl migration followed liberation of the base and only *NN'*-dibenzoylethylenediamines (XV) were obtained.*

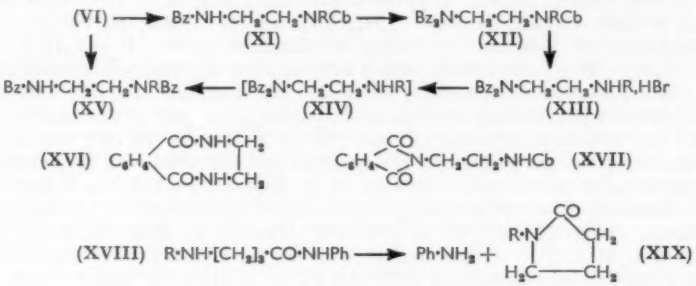
These observations prompted an investigation of the stability of *N*-2-aminoethylphthalimide which could be expected to rearrange to the diamide (XVI). Spring and Woods [14] reported, without experimental details, reactions of primary amines with *N*-2-aminoethylphthalimide, and Braun and Pinkernelle [15] prepared *N*-3-aminopropylphthalimide. In neither case, however, was the stability of the aminophthalimide

* Since this paper was submitted, Wieland and Urbach (*Annalen*, 1958, **613**, 84) have reported similar reactions of *N*-acylamides.

[12] Taschner, Kocór, and Meyer, *Roczniki Chem.*, 1952, **26**, 692.
[13] Titherley, *J.*, 1904, **85**, 1673.
[14] Spring and Woods, *Nature*, 1946, **158**, 754.
[15] Braun and Pinkernelle, *Ber.*, 1934, **67**, 1056.

indicated. Treatment of the urethane (XVII) with hydrogen bromide gave *N*-2-aminoethylphthalimide hydrobromide. Liberation of the base gave only an unidentified acid without the properties of (XVI) [16] (of doubtful structure [17]), together with a small amount of ethylenediamine.

Elimination.—Elimination of amine is the result of intramolecular aminolysis when the amino-group is in the acid moiety of the amide. Instances have been given by Barrass



and Elmore [3] who, while this work was in progress, reported the formation of the cyclic lactams from amides of basic amino-acids. In this work, the γ-alkylaminobutyranilides (XVIII; R = Ph·CH_2 or C_6H_{11}), obtained from γ-bromobutyranilide, slowly cyclised, on being heated, to *N*-alkylpyrrolid-2-ones (R = Ph·CH_2 or C_6H_{11}) with elimination of aniline. Comparison of the rates of the reactions again revealed the lowering of the nucleophilicity of the α-branched amine in spite of its greater basic strength (towards protons). Thus cyclisation of γ-benzylaminobutyranilide was complete in 1 hr. at 160° whereas that of the *cyclo*hexyl compound was incomplete after 2 hr. at 220°. Interestingly, these cyclisations are much slower than those of basic amino-acid amides.[3]

Experimental

The light petroleum used had b. p. 40—60°. Extracts were dried over Na_2SO_4.

N-Benzyloxycarbonyl-N′-phenylethylenediamine (II; R = Ph).—2-Benzyloxycarbonylaminoethyl bromide [18] (10 g.) was heated with aniline (25 ml.) in ethylene glycol (15 ml.) at 150° for 50 min. The mixture was poured into 10% aqueous sodium carbonate and extracted with benzene. Evaporation of the extracts and removal of excess of aniline under reduced pressure left the *amine* (6·5 g.), m. p. 50—52°, raised to 58° by crystallisation from benzene–light petroleum (Found: C, 71·5; H, 7·0; N, 10·6. $C_{14}H_{16}O_2N_2$ requires C, 71·1; H, 6·7; N, 10·4%).

N-Benzoyl-N′-benzyloxycarbonyl-N-phenylethylenediamine (IV; R = Ph).—Benzoylation (Schotten–Baumann) of the preceding amine gave the *amide*, m. p. 108—109° (needles from benzene–light petroleum) (Found: C, 74·0; H, 5·7. $C_{23}H_{22}O_3N_2$ requires C, 73·8; H, 5·9%).

Rearrangement of N-Benzoyl-N-phenylethylenediamine (V; R = Ph).—Treatment of the amide (IV; R = Ph) with 50% hydrogen bromide in acetic acid and addition of anhydrous ether after reaction was complete, yielded a hygroscopic hydrobromide which gave no picrate and a hygroscopic perchlorate. An aqueous solution of the hydrobromide [from 2 g. of (IV)] was basified with sodium hydroxide and extracted with chloroform. Evaporation of the extracts at room temperature and treatment of the residue with light petroleum gave *N*-benzoyl-*N′*-phenylethylenediamine (1·1 g.), m. p. 120°. Crystallisation from methanol raised the m. p. to 127°, alone or mixed with an authentic specimen.[19]

N-Benzyloxycarbonyl-N′-cyclohexylethylenediamine (II; R = C_6H_{11}).—2-Benzyloxycarbonylaminoethyl bromide (13 g.) was heated with *cyclo*hexylamine (35 ml.) at 95° for 30 min. The mixture was added to an excess of aqueous potassium hydroxide, and the suspension was

[16] Anderlini, *Gazzetta*, 1894, **24**, 401.
[17] Beilstein's "Handbuch der Organischen Chemie," Springer, Berlin, 1933, Vol. XVII, p. 480.
[18] Katchalski and Ben-Ishai, *J. Org. Chem.*, 1950, **15**, 1067.
[19] Gabriel and Stelzner, *Ber.*, 1895, **28**, 2929.

extracted with benzene. The extracts, on being shaken with 20% hydrochloric acid (100 ml.), gave a precipitate of N-*benzyloxycarbonyl*-N′-cyclo*hexylethylenediamine hydrochloride* (14·5 g.), m. p. 179°, raised to 182° by crystallisation from ethanol (Found: C, 61·4; H, 7·9; N, 8·7. $C_{16}H_{25}O_2N_2Cl$ requires C, 61·5; H, 7·7; N, 9·0%). The *base*, liberated from the hydrochloride with aqueous sodium carbonate, had m. p. 70° (from ether) (Found: N, 10·0. $C_{16}H_{24}O_2N_2$ requires N, 10·2%).

N-*Benzoyl*-N′-*benzyloxycarbonyl*-N-cyclo*hexylethylenediamine* (IV; R = C_6H_{11}).—Treatment of the base with benzoyl chloride in pyridine gave the *amide*, m. p. 114° (from benzene–light petroleum) (Found: C, 73·2; H, 7·6. $C_{23}H_{28}O_3N_2$ requires C, 72·6; H, 7·4%).

Rearrangement of N-*Benzoyl*-N-cyclo*hexylethylenediamine* (V; R = C_6H_{11}).—The amide (IV; R = C_6H_{11}) (10 g.) was treated with a 50% solution of hydrogen bromide in acetic acid (25 ml.). When reaction was complete, water (100 ml.) and ether (200 ml.) were added. The aqueous layer was separated and divided into two equal parts: part (i) was basified with sodium hydroxide, and toluene-*p*-sulphonyl chloride (10 g.) in acetone (20 ml.) was added. When reaction was complete, the suspension was acidified and extracted with chloroform. Evaporation of the extracts gave a residue (5·9 g.), m. p. 143—150°, which was boiled with ethanol (25 ml.). Filtration of the cold mixture gave N-*benzoyl*-N-cyclo*hexyl*-N′N′-*ditoluene*-p-*sulphonylethylenediamine* (VIII) (3·6 g.), m. p. 175—176° (Found: C, 63·0; H, 6·2. $C_{29}H_{34}O_5N_2S_2$ requires C, 62·9; H, 6·1%). Concentration of the mother-liquors gave N-*benzoyl*-N-cyclo*hexyl*-N′-*toluene*-p-*sulphonylethylenediamine* (VII) (1·2 g.), m. p. 117—119° raised to 121—122° (from benzene–light petroleum) (Found: C, 66·0; H, 6·6. $C_{22}H_{28}O_3N_2S$ requires C, 66·0; H, 7·0%). The residual solution was evaporated to dryness. The residue (0·7 g.) had m. p. 105—106° alone or mixed with the monosulphonamide (VII) but depressed the m. p. of the sulphonamide (IX) (below). Treatment of the monosulphonamide (VII) with toluene-*p*-sulphonyl chloride gave the disulphonamide (VIII), m. p. and mixed m. p. 176°.

Part (ii) was basified similarly and extracted with benzene. The extracts were evaporated and the residue (3·4 g.) was heated at 150° for 1 hr. Subsequent treatment with toluene-*p*-sulphonyl chloride (10 g.) gave an oil (4·8 g.) which, with ethanol (10 ml.), gave the disulphonamide (VIII) (0·6 g.), m. p. and mixed m. p. 165—168°. The mother-liquors, in benzene (24 ml.), were poured on an alumina column (25 × 2 cm.). Elution with 1 : 1 benzene–chloroform gave N′-*benzoyl*-N-cyclo*hexyl*-N-*toluene*-p-*sulphonylethylenediamine* (IX) (2·9 g.), m. p. 94—97°, raised to 113—114° (from ethanol) (Found: C, 66·4; H, 7·1%). Further elution gave only yellow gums.

N′-*Benzyloxycarbonyl*-N-cyclo*hexyl*-N-*toluene*-p-*sulphonylethylenediamine* (X).—The urethane (II; R = C_6H_{11}) with toluene-*p*-sulphonyl chloride and aqueous sodium hydroxide gave the *sulphonamide*, m. p. 94° (from ethanol) (Found: C, 64·6; H, 7·1. $C_{23}H_{30}O_4N_2S$ requires C, 64·3; H, 7·0%). Removal of the benzyloxycarbonyl group (hydrogen bromide in acetic acid) and subsequent benzoylation of the base (Schotten–Baumann) gave the sulphonamide (IX), m. p. and mixed m. p. 113—114°.

N-*Benzoyl*-N′-cyclo*hexylethylenediamine* (VI; R = C_6H_{11}).—*N*-2-Bromoethylbenzamide [19] and *cyclo*hexylamine (40 ml.) were kept at 100° for 50 min. The mixture was poured into dilute hydrochloric acid and extracted with benzene. The aqueous layer was basified with sodium hydroxide and re-extracted with benzene. Distillation of the residue after evaporation of the extracts gave (i) 2-phenyloxazoline (6 g.), b. p. 80°/0·1 mm. (picrate, m. p. 183°; lit.,[20] m. p. 186°), and (ii) the *amino-amide* (5 g.), b. p. 167°/0·01 mm. (Found: N, 11·4. $C_{15}H_{22}ON_2$ requires N, 11·4%). In contact with air the latter compound gave a carbonate, m. p. 58—62°, but of variable composition (Found: N, 10·6, 9·8, 9·4. Calc. for $C_{15}H_{22}ON_2,\frac{1}{2}H_2CO_3$: N, 10·1%). Treatment with toluene-*p*-sulphonyl chloride gave the sulphonamide (IX), m. p. and mixed m. p. 113—114°.

Formation of N-cyclo*Hexyltetrahydro*-2-*oxoglyoxaline* (III).—The base (II; R = C_6H_{11}) (1 g.) was heated at 180°/20 mm. Benzyl alcohol (0·4 g.) slowly distilled (b. p. *ca.* 90°; *p*-nitrobenzoate, m. p. and mixed m. p. 83—84°). The residual glyoxaline derivative (0·6 g.) had m. p. 170·5° (from benzene–light petroleum) (Found: N, 16·3. Calc. for $C_9H_{16}ON_2$: N, 16·7%). Abramovitch [21] gives m. p. 166—168°.

N′-*Benzoyl*-N-*benzyloxycarbonyl*-N-cyclo*hexylethylenediamine* (XI; R = C_6H_{11}).—*N*-Benzoyl-*N′-cyclo*hexylethylenediamine (3·8 g.) and benzyl chloroformate (3·8 ml.) were shaken with 10%

[20] Goldberg and Kelly, *J.*, 1948, 1919.
[21] Abramovitch, U.S.P. 2,518,264.

aqueous sodium carbonate. Excess of the chloroformate was destroyed by addition of ethereal pyridine. Evaporation of the ethereal extract and distillation of the residue gave the *amido-urethane* (5·7 g.), b. p. 230°/0·02 mm. (Found: C, 72·1; H, 7·3. $C_{23}H_{28}O_3N_2$ requires C, 72·6; H, 7·4%).

NN-*Dibenzoyl*-N′-cyclo*hexylethylenediamine Hydrobromide* (XIII; R = C_6H_{11}).—The amido-urethane (4 g.) in pyridine (10 ml.) was heated with benzoyl chloride (3 ml.) at 100° for 30 min. The mixture was poured into water and extracted with benzene. The extracts were washed successively with 10% aqueous sodium carbonate, dilute hydrochloric acid, and water. Evaporation of the extracts gave a red oil which was treated directly with a 50% solution of hydrogen bromide in acetic acid (15 ml.). When reaction was complete, addition of ether precipitated the *hydrobromide* (4·5 g.), m. p. 190—192° raised, on crystallisation from methanol, to 201—202° (Found: C, 61·2; H, 6·2. $C_{22}H_{27}O_2N_2Br$ requires C, 61·2; H, 6·3%).

Rearrangement of the Base.—The hydrobromide (2·4 g.), suspended in ethanol (5 ml.), was added to 10% aqueous sodium carbonate (20 ml.). The mixture was diluted with water and filtered. The residue, NN′-*dibenzoyl*-N-cyclo*hexylethylenediamine* (1·8 g.), had m. p. 203° raised to 205—206° (from ethanol) (Found: C, 75·0; H, 7·4. $C_{22}H_{26}O_2N_2$ requires C, 75·4; H, 7·4%). The m. p. was undepressed on admixture with the compound, m. p. 205—206°, obtained by benzoylation of *N*-benzoyl-*N*′-*cyclo*hexylethylenediamine (VI).

N′-*Benzoyl*-N-*benzyloxycarbonyl*-N-*phenylethylenediamine* (XI; R = Ph).—Treatment of *N*-benzoyl-*N*′-phenylethylenediamine with benzyl chloroformate as for the *cyclo*hexyl compound gave the *amido-urethane*, m. p. 80° (from benzene–light petroleum) (Found: C, 73·5; H, 6·1; N, 7·3. $C_{23}H_{22}O_3N_2$ requires C, 73·8; H, 5·9; N, 7·5%).

NN-*Dibenzoyl*-N′-*benzyloxycarbonyl*-N′-*phenylethylenediamine* (XII; R = Ph).—Treatment of the previous compound with benzoyl chloride in pyridine at 100° gav ethe NN-*dibenzoyl-amide* (70%), m. p. 133—134° (from ethanol) (Found: C, 75·6; H, 5·4. $C_{30}H_{26}O_4N_2$ requires C, 75·2; H, 5·4%). Treatment of this compound with hydrogen bromide–acetic acid gave NN-*dibenzoyl*-N′-*phenylethylenediamine hydrobromide* (XIII; R = Ph) (80%), m. p. 143° (from ethanol–ether) (Found: C, 62·3; H, 5·3. $C_{22}H_{21}O_2N_2Br$ requires C, 62·1; H, 4·9%).

Rearrangement of the Base.—20% Aqueous sodium hydroxide (5 ml.) was added to the preceding hydrobromide (2 g.) in ethanol (10 ml.), and the mixture was immediately poured into water (400 ml.). Part of the oil which separated was removed and it subsequently solidified (m. p. 143—147°). The remainder was extracted with chloroform. Evaporation of the extracts gave *NN*′-dibenzoyl-*N*-phenylethylenediamine (1·5 g.), m. p. 150° alone or mixed either with an authentic specimen, m. p. 151° (lit.,[19] 147·5°), or with the material of m. p. 143—147°.

N-2-*Benzyloxycarbonylaminoethylphthalimide* (XVII).—Potassium phthalimide (13 g.) and *N*-2-benzyloxycarbonylaminoethyl bromide (21 g.) were heated in xylene (50 ml.) for 5 hr. at 170°. Light petroleum (250 ml.) was added and the suspension was filtered. The residue was washed with water and crystallisation from ethanol gave the *urethane* (6·9 g.), m. p. 166—167° (Found: C, 67·2; H, 4·8. $C_{18}H_{16}O_4N_2$ requires C, 66·7; H, 4·9%).

N-2-*Aminoethylphthalimide.*—Treatment of the urethane with hydrogen bromide gave N-2-*aminoethylphthalimide hydrobromide*, m. p. 272° (from ethanol–ether) (Found: C, 44·5; H, 4·1. $C_{10}H_{11}O_2N_2Br$ requires C, 44·4; H, 3·9%). The hydrobromide (1·3 g.) in water (20 ml.) was treated with 10% aqueous sodium carbonate (10 ml.). The mixture was set aside for 24 hr., then filtration gave a trace of residue which sintered at 275°. The filtrate was treated with an excess of benzoyl chloride, and the product was extracted with chloroform. Evaporation of the extracts gave *NN*′-dibenzoylethylenediamine (0·1 g.), m. p. and mixed m. p. 243—247°. The aqueous solution, acidified and extraction with ether, yielded only benzoic acid, m. p. and mixed m. p. 120°. The residual aqueous solution was basified with sodium carbonate and evaporated to dryness. The residue was extracted with boiling absolute ethanol (50 ml.). Evaporation of the extracts gave a hygroscopic residue (1·3 g.) which gave an *S*-benzylthiuronium salt, m. p. 152° (from ethanol–ether) (Found: C, 60·7; H, 5·0; N, 11·4; S, 6·5. Calc. for $C_{25}H_{24}O_5N_4S$: C, 60·9; H, 4·9; N, 11·4; S, 6·5%).

γ-Bromobutyranilide.—γ-Bromobutyric acid, obtained by hydrolysis of γ-butyrolactone with 60% hydrobromic acid,[22] had b. p. 142°/25 mm. (lit.,[23] b. p. 126—129°/7 mm.). γ-Bromobutyryl chloride (from 31·5 g. of acid) in benzene was treated with aniline (38 g.). When reaction was complete, the mixture was washed with hydrochloric acid, and evaporation of the benzene

[22] Henry, *Compt. rend.*, 1886, **102**, 368.
[23] Marvel and Birkhimer, *J. Amer. Chem. Soc.*, 1929, **51**, 260.

solution under reduced pressure gave the *anilide* (34 g.), m. p. 65—67°, raised to 73—74° (from benzene–light petroleum) (Found: C, 49·8; H, 4·9. $C_{10}H_{12}ONBr$ requires C, 49·6; H, 5·0%).

γ-cyclo*Hexylaminobutyranilide* (XVIII; R = C_6H_{11}).—γ-Bromobutyranilide (34 g.) and *cyclo*hexylamine (60 ml.) were kept at 100° for 50 min. In a preliminary experiment, addition of ether to the mixture gave a precipitate which was washed with water and crystallised from ethanol, to give γ-cyclo*hexylaminobutyranilide hydrobromide*, m. p. 194—195° (Found: C, 56·5; H, 7·3; N, 8·3. $C_{16}H_{25}ON_2Br$ requires C, 56·4; H, 7·1; N, 8·2%). In subsequent experiments, the mixture was poured into 10% aqueous potassium hydroxide (200 ml.), and the suspension was extracted with benzene. The benzene extracts, on being shaken with concentrated hydrochloric acid (75 ml.), gave a precipitate of the *hydrochloride* (17·5 g.), m. p. 226° (from ethanol) (Found: Cl, 12·3. $C_{16}H_{25}ON_2Cl$ requires Cl, 12·0%). Treatment of the hydrochloride with saturated aqueous potassium bromide gave the hydrobromide, m. p. and mixed m. p. 194—195°. The *base*, liberated with aqueous sodium carbonate, had m. p. 83—84° (Found: C, 73·8; H, 8·9; N, 11·1. $C_{16}H_{24}ON_2$ requires C, 73·9; H, 9·3; N, 10·8%).

Formation of N-cyclo*Hexylpyrrolid-2-one*.—γ-*cyclo*Hexylaminobutyranilide (4 g.) was heated at 220°/20 mm. After 2 hr. the distillate was redistilled to give (i) aniline (0·7 g.), b. p. 78°/7 mm., n_D^{15} 1·5860 (benzanilide, m. p. and mixed m. p. 166°), and (ii) N-cyclo*hexylpyrrolid-2-one* (1·4 g.), b. p. 154°/7 mm., n_D^{15} 1·5043 (Found: C, 71·9; H, 10·3; N, 8·2. $C_{10}H_{17}ON$ requires C, 71·9; H, 10·2; N, 8·4%).

Cyclisation of γ-Benzylaminobutyranilide.—γ-Bromobutyranilide (19 g.) and benzylamine (35 ml.) were kept at 100° for 30 min. The mixture was treated as for the *cyclo*hexyl compound; the acid extracts were basified and extracted with benzene. The benzene extracts were evaporated and the residue, after removal of excess of benzylamine under reduced pressure, was dissolved in ether. Saturation of the solution with hydrogen chloride gave a precipitate which was filtered off and washed sparingly with water. The residue, *γ-benzylaminobutyranilide hydrochloride* (3·4 g.), had m. p. 212—213° (from ethanol–ethyl acetate) (Found: C, 66·8; H, 7·1; Cl, 12·2. $C_{17}H_{21}ON_2Cl$ requires C, 67·0; H, 6·9; Cl, 11·7%). The base (2·6 g.), extracted from a basified aqueous solution of the hydrochloride with chloroform, was heated at 160°/7 mm. During 1 hr., aniline (0·8 g.), b. p. 88°/7 mm., n_D^{18} 1·5827, distilled (benzanilide, m. p. and mixed m. p. 166°). The residue (1·8 g.) was distilled to give *N*-benzylpyrrolid-2-one (1·7 g.), b. p. 180°/10 mm., n_D^{22} 1·5490 (Found: N, 7·8. Calc. for $C_{11}H_{13}ON$: N, 8·0%). Hanford and Adams [24] give b. p. 122°/2 mm., n_D^{20} 1·5570.

The author is grateful to Professor E. L. Hirst, F.R.S., for his interest and encouragement, and Dr. D. M. W. Anderson is thanked for infrared spectrographic work. This investigation was carried out during the tenure of an I.C.I. Fellowship.

Department of Chemistry, University of Edinburgh. [*Received, August 1st*, 1958.]

[24] Hanford and Adams, *J. Amer. Chem. Soc.*, 1935, **57**, 921.

---

915. *Infrared Spectra and Hydrogen Bonding in the Nickel–Dimethylglyoxime and Related Complexes.*

By R. Blinc and D. Hadži.

Infrared spectra of dimethylglyoxime derivatives of Ni, Pd, Pt, and Cu, of the Ni and Pd complexes of *cyclo*hexane-1 : 2-dione dioxime, and of sodium and potassium hydrogen dimethylglyoxime derivatives were investigated. Assignments have been made as follows: νOH 2300—2900, δOH 1650—1800, νC=N 1500—1600, νN–O near 1240 and 1000, γOH 820—930 cm.$^{-1}$. It is concluded that the hydrogen bond in these complexes cannot be of the symmetrical type as suggested by Rundle and Parasol.[1]

Since the spectroscopic and *X*-ray work by Rundle and Parasol [1] and Rundle and Godycki [2] have been published, it has been generally accepted that the hydrogen bonds in nickel–dimethylglyoxime and some related complexes are probably symmetrical in the sense

[1] Rundle and Parasol, *J. Chem. Phys.*, 1952, **20**, 1487.
[2] Rundle and Godycki, *Acta Cryst.*, 1953, **6**, 487.

that the protons occupy a central position between the oxygen atoms and that they move in a single minimum potential trough. This assumption was based on the apparent centrosymmetric structure of the nickel complex, the short O–O distance (2·44 Å), and the OH stretching frequency at 1775 cm.$^{-1}$. No direct location of the protons has been carried out and the spectrum has not been analysed in detail. The band mentioned above was assigned only on the ground of its disappearance after deuteration. In view of the importance of the existence of symmetrical hydrogen bonds in general and its bearing upon the character of the metal–nitrogen linkage in the glyoximates we re-investigated this problem.

Infrared spectra of dimethylglyoxime derivatives of Ni, Pd, Pt, Cu, and of *cyclo*hexane-1 : 2-dione dioxime complexes with Ni and Pd were studied and the important bands were assigned. To facilitate the assignments, sodium and potassium hydrogen dimethylglyoxime derivatives were prepared and their spectra recorded. These two salts have not been so far described. Spectra of deuterated Ni–, Pd–, and Na–dimethylglyoxime complexes were also obtained.

Results

The Bands between 2000 *and* 3000 *cm.*$^{-1}$.—All the spectra of the complexes investigated contain a band near 2340 cm.$^{-1}$ (Figs. 1, 3, 4, 6, 7, 8). It is of variable intensity, being very weak in nos. 1 and 3 but strong in no. 8, and very broad. The latter property has to be borne in mind when considering the frequencies listed in the Table. In the spectrum of the copper–

Infrared absorption frequencies (cm.$^{-1}$*) of some metal–oxime complexes and salts.*

	νOH	νOD	δOH	δOD	νC=N(H)	νC=N(D)	ν′C=N	νNO	ν′NO	γOH
Dimethylglyoxime complexes										
Ni ...	2350	1810, 1910	1780	1265(?)	1560	1600	?	1235	1100	900—950(?)
Pd ...	2340	1830, 1970	1710	1210	1550	1610	1500	1250	1090	910
Na ...	3020	2340	1650	1237	1510	1540	—	990	922	815
K	3030	—	1650	—	1490	—	—	1010	930	835
cyclo*Hexane*-1 : 2-*dione dioxime complexes*										
Ni ...	2380	—	1670	—	1570	—	?	1235	990	950(?)
Pd ...	2380	—	1650	—	1540	—	1495	1245	1065	930
Pt ...	2350	—	1720	—	1550	—	1495	1260	1090	905
Cu ...	2340, 2650	—	1820	—	1590	—	1540	1210	1060	860

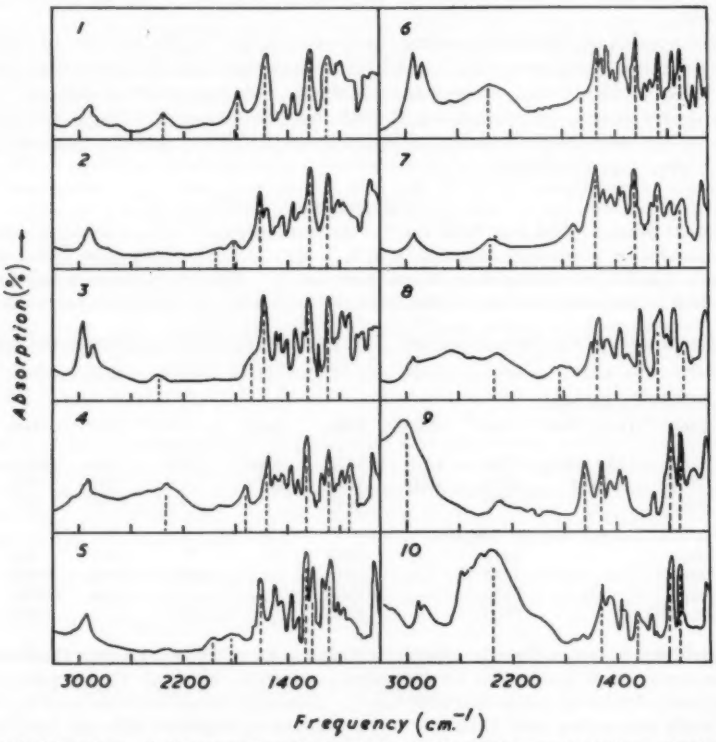
dimethylglyoxime complex there is another, stronger peak at 2650 cm.$^{-1}$ and there seem to be higher-frequency weak bands also for the other complexes, although they appear only as a broadened base of the CH_3-bands near 2930 cm.$^{-1}$. This band should be considered in connection with the weak absorption near 1910 cm.$^{-1}$ which shows up together with the band near 1820 cm.$^{-1}$ in the spectra of deuterated nickel– and palladium–dimethylglyoxime complexes. The latter band is the deuterium analogue of the band at 2340 cm.$^{-1}$ which disappears on deuteration. The spectra of the sodium and the potassium derivative (Fig. 9; the two are very similar) contain very strong and broad bands culminating at 3000 cm.$^{-1}$.

The Band between 1600 *and* 1800 *cm.*$^{-1}$.—This band varies in position and intensity in different complexes. It appears as a shoulder in spectra nos. 3 and 6, but is well developed in no. 9. It is absent from the spectra of the deuterated compounds, which contain instead a new band near 1220 cm.$^{-1}$. With the deuterated nickel complex (Fig. 2) this band does not appear clearly, but it might be hidden under the base of the strong band at 1250 cm.$^{-1}$.

The Bands between 1600 *and* 700 *cm.*$^{-1}$.—Several characteristic features appear rather consistently in this region. There is one medium or very strong band between 1500 and 1570 cm.$^{-1}$ which is shifted slightly to higher frequencies on deuteration (up to 100 cm.$^{-1}$). In some complexes there is also a weaker band near 1500 cm.$^{-1}$, which is stronger after deuteration (cf. nos. 4 and 5) but is not observed for either of the nickel complexes. There are two strong bands which appear with little changed frequency in the spectra of the complexes (near 1230 and 1050 cm.$^{-1}$). A similar pair appears for the sodium and the potassium salt at lower frequencies. Finally, a very broad band should be mentioned, normally near 900 cm.$^{-1}$ but absent from the spectra of the deuterated compounds. It is difficult to locate this band for either

of the nickel complexes because of the particularly strong, diffuse background absorption which extends from about 1500 cm.$^{-1}$ to the end of the region investigated. This background absorption seems to be lower for the deuterated complex, a phenomenon observed [3] in several spectra of substances containing very strong hydrogen bonds, *e.g.*, potassium dihydrogen phosphate and arsenate.

FIGS. 1—10. *Infrared spectra of some metal–oxime complexes and salts (drawings combined from mulls with Nujol and hexachlorobutadiene).*



1, Ni–dimethylglyoxime; 2, the same, but deuterated; 3, Ni–*cyclo*hexane-1 : 2-dione dioxime; 4, Pd–dimethylglyoxime; 5, the same, but deuterated; 6, Pd–*cyclo*hexane-1 : 2-dione dioxime; 7, Pt–dimethylglyoxime; 8, Cu–dimethylglyoxime; 9, Na hydrogen glyoxime derivative; 10, the same, but deuterated.

DISCUSSION

There is no doubt that the band near 2340 cm.$^{-1}$ belongs to the OH stretching vibration, as do the higher-frequency bands mentioned. The differences in the intensities of these bands seem to be connected in some way with the nature of the metal. Their weakness, particularly in the spectrum of both nickel complexes, may explain the failure of other investigators to notice them. The previous assignment [1] of the band near 1700 cm.$^{-1}$ to the OH stretching appears untenable in view of the present results. In principle the appearance of two OH bands could also be admitted and explained by the splitting of the vibrational levels due to the proton tunnelling,[4] but in the present case strong arguments

[3] Blinc and Hadži, *Mol. Phys.*, 1958, in the press.
[4] Blinc and Hadži, " Hydrogen Bonding," Pergamon Press, London, in the press.

against the assignment of the 1700 cm.$^{-1}$ band to one of the OH stretchings can be brought. If the bands at 2340 and 1710 cm.$^{-1}$ were due to splitting of the OH vibrational levels, deuteration should strongly reduce the extent of splitting. The spectrum of the deuterated palladium–dimethylglyoxime complex shows that this is not the case. The appearance of the band near 1650 cm.$^{-1}$ in the spectra of the potassium and the sodium salt and its shift on deuteration of the latter, similar to that with the palladium complex, also provide a strong argument against this supposition. Comparison of the present spectra with those observed [3] in the series of ferroelectric compounds of the type of KH_2PO_4, where the split OH bands are due to the tunnelling, also suports the same conclusion. In KH_2PO_4, the two OH bands were found at 2750 and 2400 cm.$^{-1}$, the O–O distance [5] (2·49 Å) being only slightly longer than, *e.g.*, in the palladium–dimethylglyoxime complex. On the other hand, the shifts on deuteration from about 1700 to 1230 cm.$^{-1}$ indicate that these bands are due to OH and OD deformation vibrations. Similar frequencies for this vibration have been found [3] for KH_2PO_4 and related compounds. The very high frequency and low intensity of the band near 1820 cm.$^{-1}$ in the spectrum of the copper–dimethylglyoxime complex causes some doubt whether this band is analogous to that just discussed for other complexes: the particular intensity of the νOH band in the copper derivatives places this complex somewhat outside the group.

The band near 1550 cm.$^{-1}$ has been assigned by Rundle and Parasol [1] to the N–O stretching vibration. In organic nitroso-compounds the νN=O stretching band has been found [6] to vary in frequency within rather large limits, 1450—1600 cm.$^{-1}$, its position depending to some extent upon the double-bond character of the linkage.[7] Thus, Rundle and Parasol's assignment implies a nearly pure double band which contradicts Rundle and Godycki's *X*-ray results.[2] The bond length (1·38 Å) indicates no shortening of the N–O bond compared with, *e.g.*, that in a hydroxylamine *O*-ether [8] (1·37 Å). On the other hand, the N–O bond in the nickel–dimethylglyoxime complex seems to be much longer [9] than the N–O bond in iodonitrosobenzene (1·24 Å). Thus, we should look for the N–O stretching band at much lower frequencies. For simple oximes, it appears [10] between 930 and 960 cm.$^{-1}$. For quinone oximes [11] it is at somewhat higher frequencies, near 1000 cm.$^{-1}$, probably owing to the increase in double-bond character because of resonance. Salt formation may also increase the frequency, and the bands near 930 and 1000 cm.$^{-1}$ in the spectra of the potassium and the sodium derivative are obviously due to the νN–O vibrations. For these two salts the two N–O bonds are probably unequal, because one OH group is ionized, so that the two band frequencies appear. Salt formation enhances the resonance in the quinone oximes and we find for their salts a strong band near 1200 cm.$^{-1}$ which is apparently due to the altered N–O linkage.[11] Thus it appears reasonable to assign the bands near 1080 and 1240 cm.$^{-1}$ in the spectra of the present complexes to the N–O stretching modes. The existence of two bands may have two explanations. They may be due to two unequal N–O linkages, as have been found by Rundle and Godycki.[2] However, the difference in the bond lengths is declared insignificant by these authors and indeed it would be incompatible with the symmetry of the complex. The other explanation is very straightforward. Considering only the skeleton of the complex, consisting of four each of C, N, and O atoms and having the symmetry D_{2h}, we may expect two N–O and two C=N infrared-active vibrations of the B_{2u} and B_{3u} type,* respectively. If the bands near 1080 and 1240 cm.$^{-1}$ are assigned to the N–O stretching vibrations, the bands between 1500 and 1600 cm.$^{-1}$ are necessarily ascribed to the C=N stretching vibrations. The

* Designated ν and ν′ in the Table.

[5] Bacon and Pease, *Proc. Roy. Soc. A.*, 1953, **220**, 397.
[6] Bellamy, " The Infra-Red Spectra of Complex Molecules," Methuen, London, 1953, p. 254.
[7] Lüttke, *J. Phys. Radium*, 1954, **15**, 633.
[8] Kitaigorodskii, " Org. Kristallokhimya," Akad. Nauk S.S.S.R., Moscow, 1955, p. 9.
[9] Webster, *J.*, 1956, 2841.
[10] Palm and Werbin, *Canad. J. Chem.*, 1954, **32**, 858.
[11] Hadži, *J.*, 1956, 2725.

corresponding bands in the spectra of simple oximes appear [12] between 1620 and 1660 cm.$^{-1}$. Resonance, with consequent decrease of the double-bond character, may produce a lowering of the frequency such as is observed [11] in the quinone oxime spectra. The C=N bond lengths (1·20 and 1·25 Å) found by Rundle and Godycki [2] for the nickel–dimethylglyoxime complex are compatible with the present frequency. The shift of the νC=N band to higher frequency after deuteration is explained by interaction with the nearby δOH vibration: this vibration, being of higher frequency, " repels " the C=N frequency and when the former is removed by deuteration, the C=N frequency returns to its undisturbed value. The shift in the opposite direction upon deuteration has been observed [11] in the quinone oxime spectra, but in these the δOH had a lower frequency than the νC=N vibration.

Assignment of the band near 960 cm.$^{-1}$ presents no difficulties: its disappearance upon deuteration and original shape suggest that it is due to the γOH (out-of-plane) deformation.

Hydrogen Bonding.—The high νOH frequency seems at first glance not to accord with the short O–O distance found by Rundle and Godycki.[2] However, the usual relations between O–O distance and OH frequency hold only for straight hydrogen bonds.[13] It is very probable that the protons in the nickel–dimethylglyoxime and related complexes are not situated on the line connecting the oxygen atoms and thus their frequency does not fit these relations.

In view of the above results, it seems that the hydrogen bonds in the complexes investigated are not of the symmetrical type, in the sense that the proton does not occupy a central position between two oxygen atoms. The observed symmetry of the nickel– and the palladium–dimethylglyoxime complex may be of a statistical character, which would imply that the protons are rapidly changing their position from near one oxygen atom to near the other. The potential barrier separating the two potential minima is probably very small, so this can be considered as a tunnelling of the protons. If this were so, the vibrational levels should be split. We may assume that the hydroxyl bands at 2340 and ~2900 cm.$^{-1}$ are due to this splitting. However, the existence of the latter band is not beyond doubt, and thus the spectrum does not clearly either prove of disprove the existence of the tunnelling, although this appears very probable on general grounds.

Experimental

The complexes were prepared by standard methods and recrystallised from nitrobenzene. The potassium and the sodium complex were prepared by adding ethanolic potassium hydroxide and aqueous sodium hydroxide, respectively, to ethanolic dimethylglyoxime. The metal hydrogen glyoxime derivatives were precipitated immediately, and neutralisation could not be achieved even if a large surplus of alkali was used. The derivatives were recrystallised several times from ethanol. The potassium derivative was analysed for potassium. No further characterisation, other than the infrared spectrum, was undertaken. Deuteration was by dissolving the substances in boiling dioxan and adding deuterium oxide until crystallisation had set in. The crystalline precipitate was filtered off and dried, precautions being taken against contamination with atmospheric moisture. The spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer, equipped with a rock-salt prism. The samples were mulls in Nujol or hexachlorobutadiene.

The authors are grateful to Misses M. Žitko and T. Berginc for the preparation of substances.

University Chemical Laboratory and Institute B. Kidrič, Ljubljana.
[Present address (R. B.): Institute J. Štefan, Ljubljana.] [*Received, August 5th*, 1958.]

[12] Palm and Werbin, *Canad. J. Chem.*, 1953, **31**, 1004.
[13] Lippincott and Schroeder, *J. Chem. Phys.*, 1955, **23**, 1099.

XUM

916. *Some Synthetic Cysteinyl Peptides.*

By H. S. Bachelard and V. M. Trikojus.

The syntheses are described of a number of peptides of cysteine, suitable as substrates for studies of the specificity of the enzyme, thyroid " cysteinyl-tyrosinase."

During investigations in this Department on the separation of the components of the proteolytic system of the thyroid gland, a proteinase, substantially purified, was isolated.[1] This fraction also exhibited limited peptidase activity, when tested with a range of peptides, and appeared to hydrolyse specifically the peptide bond linking cysteine and tyrosine, in particular that of L-cysteinyl-L-tyrosine. However, unlike pepsin which also hydrolyses cysteinyltyrosine,[2] thyroid " cysteinyltyrosinase " activity did not seem to be a property of the proteinase molecule.[1] This has been confirmed by its separation from the proteinase by column electrophoresis.[3]

Apart from its interest in thyroid biochemistry, an enzyme specifically hydrolysing peptides at the cysteinyl (cystinyl) link should prove of value in the determination of protein structure. For the further elucidation of the specificity requirements of this enzyme several new peptides containing cysteine have been synthesised, of which the following are described in this paper: L-cysteinyl-L-phenylalanine; L-cysteinyl-L-tyrosine amide; L-leucyl-L-cysteine; L-leucyl-L-cysteinyl-L-tyrosine amide; glycyl-L-leucyl-L-cysteinyl-L-tyrosine amide.

As an additional check on the products obtained, two condensation procedures were usually employed. These were the azide method [4] and the mixed anhydride reaction.[5] Protection of free amino- and thiol groups followed the methods described by Bergmann and Zervas [6] and Wood and du Vigneaud; [7] protecting groups were removed by sodium and liquid ammonia,[8] and an *N*-benzyloxycarbonyl group preferentially by acetic acid saturated with hydrogen bromide.[9]

Isolation and purification of the basic peptides (those containing a terminal amide group) presented difficulties. They were very soluble in water and rapidly lost titratable thiol activity [10] during attempts to recrystallise them from this or other solvents. In consequence, after reductive removal of the protecting groups, the free peptides were precipitated as the mercaptides with modified Hopkins's reagent.[11] Benesch and Benesch [12] have described the formation of glutathione from its mercaptide in the electrolytic de-salter[13] as modified by Dent,[14] but the direct application of this technique was found to give low yields in the cases under discussion, largely owing to the considerable frothing. However, if the mercaptides were first decomposed with hydrogen sulphide and the filtered solutions de-salted and immediately dried in the frozen state, white powders were obtained, virtually uncontaminated by salts or trace metals and with high thiol titration values. This procedure may be of value in the isolation of other sensitive peptides.

[1] Laver and Trikojus, *Biochim. Biophys. Acta*, 1956, **20**, 444.
[2] Harington and Pitt Rivers, *Biochem. J.*, 1944, **38**, 417.
[3] McQuillan, unpublished experiments.
[4] Curtius, *Ber.*, 1902, **35**, 3226.
[5] Boissonas, *Helv. Chim. Acta*, 1951, **34**, 874.
[6] Bergmann and Zervas, *Ber.*, 1932, **65**, 1192.
[7] Wood and du Vigneaud, *J. Biol. Chem.*, 1939, **130**, 109.
[8] Sifferd and du Vigneaud, *ibid.*, 1935, **108**, 753.
[9] Ben Ishai and Berger, *J. Org. Chem.*, 1952, **17**, 1564.
[10] Benesch and Benesch, *Biochim. Biophys. Acta*, 1957, **23**, 643.
[11] Kendall, McKenzie, and Mason, *J. Biol. Chem.*, 1929, **84**, 657.
[12] Benesch and Benesch, *Biochim. Biophys. Acta*, 1957, **23**, 658.
[13] Consden, Gordon, and Martin, *Biochem. J.*, 1947, **41**, 590.
[14] Dent, " Recent Advances in Clinical Pathology," Churchill, London, 1951, 2nd edn., p. 252.

XUM

Enzyme–substrate studies with the above-mentioned and related peptides will be reported elsewhere.

Experimental

All chemicals were purified by the usual methods. Amino-acids were from Lights or B.D.H. Microanalyses were carried out by Dr. W. Zimmermann, C.S.I.R.O. Microanalytical Laboratory, University of Melbourne. Optical activity was measured in a tube 10 cm. × 3 mm., with a polarimeter of the Lippich type.

S-*Benzyl*-N-*benzyloxycarbonyl*-L-*cysteinyl*-L-*phenylalanine Methyl Ester.*—(a) ***Mixed anhydride method.*** To a cold solution of *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteine [15] (4·13 g.) in chloroform (50 ml.) and triethylamine (1·58 ml.) was added freshly distilled ethyl chloroformate (1·135 ml.). The mixture was kept at 0° for 20 min., and a chilled solution of L-phenylalanine methyl ester (from 2·58 g. of the hydrochloride) in chloroform (50 ml.) was slowly added. After being kept at 0° for 30 min., overnight at room temperature, and finally at 50° for 3 hr., the solution was washed successively with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4). Removal of solvents under reduced pressure resulted in an oil which produced white needles (from methanol) (60%), m. p. 103—105°. The *methyl ester*, recrystallised from methanol, had m. p. 105—105·5°, $[\alpha]_D^{24}$ −34·7° (*c* 1·5 in 95% ethanol) (Found: C, 66·7; H, 6·0; N, 5·5. $C_{28}H_{30}O_5N_2S$ requires C, 66·4; H, 6·0; N, 5·5%).

(b) ***Azide method.*** To an ethyl acetate solution of *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteine azide, prepared from the hydrazide [2] (1·79 g.), was added a cold solution of L-phenylalanine methyl ester (from 1·08 g. of the hydrochloride) in chloroform (20 ml.). The mixture was kept at 3° for 2 days and the solvents were removed under reduced pressure, leaving an oil which produced needles (from methanol) (60%), m. p. 103—104°. The products from (*a*) and (*b*) proved identical by mixed melting points.

S-*Benzyl*-N-*benzyloxycarbonyl*-L-*cysteinyl*-L-*phenylalanine.*—The above methyl ester (2·2 g.) was saponified in methanol (200 ml.) with N-sodium hydroxide (14 ml.) for 24 hr. at 20°, after which the solution was adjusted to pH 6 with 5N-hydrochloric acid. On removal of most of the methanol and acidification to pH 3, the product was obtained as white needles (80%), m. p. 147—151°. The *peptide*, recrystallised twice from methanol, had m. p. 155·5°, $[\alpha]_D^{21}$ −16·5° (*c* 2 in ethanol) (Found: C, 65·9; H, 5·75; N, 5·7. $C_{27}H_{28}O_5N_2S$ requires C, 65·8; H, 5·7; N, 5·7%).

L-*Cysteinyl*-L-*phenylalanine.*—*S*-Benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-L-phenylalanine (2·0 g.) was dissolved in liquid ammonia, and small pieces of sodium were added until a permanent blue colour was obtained (0·7 g. being required). Ammonium chloride (1·8 g.) was added and the ammonia was removed. The residue was dissolved in 0·5N-sulphuric acid (35 ml.) and filtered. The mercaptide was precipitated, washed, and decomposed according to the techniques described by Harington and Pitt Rivers.[2] The aqueous peptide solution from the treatment with hydrogen sulphide was concentrated *in vacuo* to 20 ml., filtered, and electrolytically de-salted. Crystals began to grow in clusters immediately and were recrystallised three times from hot oxygen-free glass-distilled water and had m. p. >300° (65%), $[\alpha]_D^{24}$ +8·5° (*c* 2 in N-HCl) (lit.,[16] $[\alpha]_D^{25}$ −8·9°) (Found: C, 51·5; H, 6·2. Calc. for $C_{12}H_{16}O_3N_2S,\frac{1}{2}H_2O$: C, 52·0; H, 6·2%). Thiol titration [10] gave 98% of SH. The dipeptide was dried *in vacuo* at 120° to constant weight (Found: C, 53·6; H, 6·1. Calc. for $C_{12}H_{16}O_3N_2S$: C, 53·7; H, 6·0%).

After completion of this work, the synthesis of L-cysteinyl-L-phenylalanine by an alternative route, involving the catalytic hydrogenation of the corresponding cystinyl peptide, was reported.[16] The compound, however, gave the negative value for $[\alpha]_D$ cited above.

S-*Benzyl*-L-*cysteinyl*-L-*phenylalanine.*—*S*-Benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-L-phenylalanine (0·2 g.) and glacial acetic acid saturated with hydrogen bromide (2 ml.) were kept under anhydrous conditions for 30 min. at room temperature. Addition of dry ether deposited needles which were collected, washed with ether, and dissolved in water (4 ml.). Addition of ammonia (*d* 0·88) to pH 5 and concentration *in vacuo* to 2 ml. yielded an amorphous product

[15] Harington and Mead, *Biochem. J.*, 1936, **30**, 1598.
[16] Berse, Boucher, and Piche, *J. Org. Chem.*, 1957, **22**, 805.

XUM

(80%), m. p. 233—235° (decomp.). For analysis, S-*benzyl*-L-*cysteinyl*-L-*phenylalanine* was recrystallised twice from methanol to give platelets, m. p. 236° (decomp.), $[\alpha]_D^{27}$ +14·0° (*c* 1 in dimethylformamide) (Found: N, 7·5. $C_{19}H_{22}O_3N_2S$ requires N, 7·8%).

S-*Benzyl*-N-*benzyloxycarbonyl*-L-*cysteinyl*-L-*tyrosine Methyl Ester*.—*S*-Benzyl-*N*-benzyloxycarbonyl-L-cysteine azide (from the hydrazide, 8·0 g.) and L-tyrosine methyl ester (4·3 g.) were condensed by the azide method. The resultant oil was triturated with successive small aliquot parts of ether, to give needles, m. p. 92—97°. The *methyl ester*, recrystallised twice from ethanol (charcoal) (60%), had m. p. 110—111° (lit.,[17] m. p. 89°), $[\alpha]_D^{24}$ −30·5° (*c* 2 in 95% ethanol) (Found: C, 64·35; H, 5·85; N, 5·2. $C_{28}H_{30}O_6N_2S$ requires C, 64·35; H, 5·8; N, 5·35%) (lit.,[17] C, 63·5%).

S-*Benzyl*-N-*benzyloxycarbonyl*-L-*cysteinyl*-L-*tyrosine Amide*.—(*a*) *S*-Benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-L-tyrosine methyl ester (4·5 g.) was dissolved in methanol which had previously been saturated with ammonia at 0° (50 ml.). After 2 days at room temperature under anhydrous conditions, the flask contained a solid mass of white needles (70%), m. p. 196—197° (decomp.).

(*b*) *S*-Benzyl-*N*-benzyloxycarbonyl-L-cysteine hydrazide (5 g.) and L-tyrosine amide (2·55 g.) were condensed by the azide method, to give white needles (80%), m. p. 195—196° (decomp.). The *amide*, recrystallised from ethanol, had m. p. 196—196·5° (decomp.), $[\alpha]_D^{23}$ −36·0° (*c* 2 in dimethylformamide) (Found: C, 64·1; H, 5·9; N, 8·1. $C_{27}H_{29}O_5N_3S$ requires C, 63·9; H, 5·8; N, 8·3%).

(*c*) The protected dipeptide amide was also prepared by the mixed anhydride method, but the yield was only 20%. The products from all three methods were found to be identical by mixed melting points.

L-*Cysteinyl*-L-*tyrosine Amide*.—*S*-Benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-L-tyrosine amide (3·5 g.) was dissolved in liquid ammonia (300 ml.) and small pieces of sodium were added until a blue colour persisted for 30 sec. (0·95 g. being required). Ammonium chloride (2·6 g.) was added and the ammonia was removed. After dissolution of the residue in 0·5N-sulphuric acid (60 ml.) the mercaptide was precipitated with modified Hopkins's reagent [11] and decomposed with hydrogen sulphide.[3] The aqueous solution of L-*cysteinyl*-L-*tyrosine amide* was then electrolytically de-salted and freeze-dried (80%); it had m. p. 83—84° (decomp.), $[\alpha]_D^{24}$ +12·0° (*c* 2·5 in N-hydrochloric acid) (Found: C, 49·7; H, 6·1. $C_{12}H_{17}O_3N_3S$ requires C, 50·9; H, 6·05%). Thiol titration [10] gave 96% of SH. The peptide amide proved difficult to purify. White prisms obtained from methanol–ether contained only 35% of SH (by titration [10]). Attempted purifications by formation of the hydrochloride, picrate, and picrolonate were unsuccessful. When protected with *N*-ethylmaleimide,[18] the peptide behaved as a single substance on paper chromatograms in butan-1-ol–acetic acid–water (4 : 1 : 1).

S-*Benzyl*-L-*cysteinyl*-L-*tyrosine Amide*.—*S*-Benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-L-tyrosine amide (3·4 g.) and glacial acetic acid saturated with hydrogen bromide (35 ml.) were allowed to react at room temperature under anhydrous conditions for 45 min. On addition of ether (200 ml.) an oil was deposited which was washed with ether by decantation and dissolved in water (30 ml.). The product obtained on the addition of ammonia (*d* 0·88) to pH 8 had m. p. 94—96° (decomp.). The *amide* was purified by dissolving it in 0·2N-acetic acid and adjusting the pH to 8 {yield 80%, m. p. 98—98·5° (decomp.), $[\alpha]_D^{23}$ +6·0° (*c* 1 in dimethylformamide)} (Found: C, 61·1; H, 6·1. $C_{19}H_{23}O_3N_3S$ requires C, 61·1; H, 6·2%).

N-*Benzyloxycarbonyl*-L-*leucyl*-S-*benzyl*-L-*cysteinyl*-L-*tyrosine Amide*.—(a) *Mixed anhydride method*. A solution of *N*-benzyloxycarbonyl-L-leucine [19] (1·43 g.) in chloroform (25 ml.) and triethylamine (0·725 ml.) was cooled to 0°, freshly distilled ethyl chloroformate (0·525 ml.) was added dropwise with stirring, and the mixture was kept at 0° for 30 min. Then was added a cold solution of *S*-benzyl-L-cysteinyl-L-tyrosine amide (2·0 g.) in dimethylformamide (20 ml.). The whole was kept at 0° for 30 min., overnight at room temperature, and finally at 60° for 1 hr. After removal of the chloroform under reduced pressure, the crude product was precipitated with water. The *amide* recrystallised from ethanol as white needles (90%), m. p. 192—193°, $[\alpha]_D^{24}$ −21·0° (*c* 2 in dimethylformamide) (Found: C, 63·4; H, 6·5; N, 8·8. $C_{33}H_{40}O_6N_4S$ requires C, 63·8; H, 6·5; N, 9·0%).

(b) *Azide method*. An ethyl acetate extract of *N*-benzyloxycarbonyl-L-leucine azide was

[17] Boissonas, Guttman, Jaquenoud, and Waller, *Helv. Chim. Acta*, 1955, **38**, 1491.
[18] Hanes, Hird, and Isherwood, *Nature*, 1950, **166**, 288.
[19] Bergmann, Zervas, and Fruton, *J. Biol. Chem.*, 1936, **115**, 593.

prepared at 0° from the hydrazide [20] (0·5 g.), and a cold solution of *S*-benzyl-L-cysteinyl-L-tyrosine amide (0·7 g.) in dimethylformamide (5 ml.) was added. After 2 days at 3°, the product (70%), m. p. 192—193°, proved identical with that from (*a*) by mixed melting points.

L-Leucyl-L-cysteinyl-L-tyrosine Amide.—*N*-Benzyloxycarbonyl-L-leucyl-*S*-benzyl-L-cysteinyl-L-tyrosine amide (1·0 g.) was reduced in liquid ammonia with sodium (0·45 g.), and the product (65%) isolated as described for L-cysteinyl-L-tyrosine amide. The freeze-dried peptide, m. p. 171—174° (softens at 153°), $[\alpha]_D^{24}$ −1·8° (*c* 2 in N-hydrochloric acid), contained 95% of SH by titration.[10] Satisfactory analytical figures were not obtained. The difficulties of purification encountered with L-cysteinyl-L-tyrosine amide were also experienced with this peptide, which, however, behaved as a single entity, after protection with *N*-ethylmaleimide,[18] on paper chromatograms in butan-1-ol–acetic acid–water (4 : 1 : 1).

S-*Benzyl-L-cysteinyl-L-tyrosine.*—*S*-Benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-L-tyrosine [2] (0·5 g.) was treated as described previously for *S*-benzyl-L-cysteinyl-L-phenylalanine. S-*Benzyl-L-cysteinyl-L-tyrosine*, recrystallised from water (80%), had m. p. 114—115°, $[\alpha]_D^{27}$ +26·5° (*c* 1 in dimethylformamide) (Found: N, 7·3. $C_{19}H_{22}O_4N_2S$ requires N, 7·5%).

N-*Benzyloxycarbonyl-L-leucyl*-S-*benzyl-L-cysteine Ethyl Ester.*—*N*-Benzyloxycarbonyl-L-leucine [19] (1·5 g.) and *S*-benzyl-L-cysteine [2] (1·58 g.) were coupled by the mixed anhydride procedure, and the *ethyl ester* was recrystallised from ethanol (75%); it had m. p. 103·5—104°, $[\alpha]_D^{23}$ −66·5° (*c* 2 in 95% ethanol) (Found: C, 64·2; H, 7·05; N, 5·5. $C_{26}H_{34}O_5N_2S$ requires C, 64·2; H, 7·0; N, 5·75%).

N-*Benzyloxycarbonyl-L-leucyl*-S-*benzyl-L-cysteine.*—The ethyl ester was saponified as previously described; the *peptide*, recrystallised from aqueous ethanol (80%), had m. p. 157—158°, $[\alpha]_D^{22}$ −41·5° (*c* 2 in 95% ethanol) (Found: N, 5·9. $C_{24}H_{30}O_5N_2S$ requires N, 6·1%).

L-Leucyl-L-cysteine.—*N*-Benzyloxycarbonyl-L-leucyl-*S*-benzyl-L-cysteine (2·0 g.) was reduced in liquid ammonia with sodium (0·6 g.), and the product isolated as previously described for L-cysteinyl-L-phenylalanine. (Twice the expected volume, 14 ml., of the modified Hopkins' reagent [11] was required to give complete precipitation of the mercaptide.) The resultant freeze-dried powder was dissolved in oxygen-free glass-distilled water and placed over a dish of ethanol in a partially evacuated desiccator, to give spherical crystalline aggregates of *L-leucyl-L-cysteine* (45%), m. p. >250° (softens at 153°, darkens at 185°), $[\alpha]_D^{26}$ +19·5° (*c* 2 in N-hydrochloric acid) (Found: C, 44·5; H, 8·0. $C_9H_{18}O_3N_2S,\frac{1}{2}H_2O$ requires C, 44·4; H, 7·9%). The peptide was dried at 120° *in vacuo* to constant weight (Found: C, 46·5; H, 7·7. $C_9H_{18}O_3N_2S$ requires C, 46·1; H, 7·7%). Thiol titration [10] gave 95% of SH.

L-Leucyl-S-*benzyl-L-cysteinyl-L-tyrosine Amide.*—*N*-Benzyloxycarbonyl-L-leucyl-*S*-benzyl-L-cysteinyl-L-tyrosine amide (1·8 g.) was treated as described for *S*-benzyl-L-cysteinyl-L-tyrosine amide to give *L-leucyl*-S-*benzyl-L-cysteinyl-L-tyrosine amide* (85%), m. p. 192—193° (decomp.), $[\alpha]_D^{20}$ −40·5° (*c* 2 in dimethylformamide) (Found: N, 11·2. $C_{25}H_{34}O_4N_4S$ requires N, 11·5%).

N-*Benzyloxycarbonylglycyl-L-leucyl*-S-*benzyl-L-cysteinyl-L-tyrosine Amide.*—(a) *Mixed anhydride method.* A solution of *N*-benzyloxycarbonylglycine [6] (0·23 g.) in chloroform (15 ml.) and triethylamine (0·14 ml.) was cooled to 0°, and freshly distilled ethyl chloroformate (0·10 ml.) was added dropwise. The mixed anhydride solution was kept at 0° for 20 min. and a cold solution of L-leucyl-*S*-benzyl-L-cysteinyl-L-tyrosine amide (0·5 g.) in dimethylformamide (5 ml.) was added. The mixture was kept at 0° for 30 min., then overnight at room temperature, and finally at 60° for 1 hr. The chloroform was removed under reduced pressure and the product was precipitated with water. Recrystallisation from acetone gave m. p. 181—183° (70%). The *amide* was recrystallised twice from ethanol to give needles, m. p. 187—188°, $[\alpha]_D^{21}$ −57·0° (*c* 2 in dimethylformamide) (Found: N, 10·4; S, 4·5. $C_{35}H_{43}O_7N_5S$ requires N, 10·35; S, 4·7%).

(b) *Azide method.* An ethyl acetate extract of *N*-benzyloxycarbonylglycyl-L-leucine azide (from 1·0 g. of the hydrazide [21]) was condensed at 0° with *S*-benzyl-L-cysteinyl-L-tyrosine amide (1·1 g.) in dimethylformamide (10 ml.). After 2 days at 3°, the product (90%) proved identical with that obtained from the mixed anhydride procedure.

Glycyl-L-leucyl-L-cysteinyl-L-tyrosine Amide.—*N*-Benzyloxycarbonylglycyl-L-leucyl-*S*-benzyl-L-cysteinyl-L-tyrosine amide (0·45 g.) was reduced in liquid ammonia with sodium (0·18 g.), and the product was isolated as described for L-cysteinyl-L-tyrosine amide, to give glycyl-L-leucyl-L-cysteinyl-L-tyrosine amide (60%), m. p. 179—181° (softens at 168°, decomp.), $[\alpha]_D^{20}$ −39·5°

[20] Bergmann, Zervas, Fruton, Schneider, and Schleich, *J. Biol. Chem.*, 1935, **109**, 325.
[21] Harris and Fruton, *ibid.*, 1951, **188**, 251.

XUM

(*c* 2 in N-hydrochloric acid). Thiol titration [10] gave 94% of SH. Satisfactory analytical figures were not obtained. Similar difficulties of purification to those with L-cysteinyl-L-tyrosine amide were experienced. The peptide behaved as a single substance, after protection with *N*-ethylmaleimide,[10] on paper chromatograms in butan-1-ol–acetic acid–water (4 : 1 : 1). The peptide must be stored under anhydrous conditions to prevent deterioration.

We are indebted to the National Health and Medical Research Council (Australia) for a personal grant (to H. S. B.) and for financial assistance towards the cost of this investigation. We thank Dr. J. M. Swan, Wool Textile Research Laboratories, C.S.I.R.O., Melbourne, for helpful discussion.

DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF MELBOURNE,
CARLTON, N.3, VICTORIA, AUSTRALIA. [*Received, August 8th*, 1958.]

---

917. *Urinary Steroids and Related Compounds. Part II.*[1] 11 : 17-*Disubstituted Androstanes carrying no Substituent at Position* 3.

By W. KLYNE and SHEILA PALMER (*née* RIDLEY).

A series of 5α-androstane derivatives carrying no substituent at position 3 have been prepared; these compounds include 11-monosubstituted and 11 : 17-disubstituted derivatives. Their physical properties (infrared spectra and molecular rotations) provide reference data for the assessment of vicinal action between positions 11 and 17.

PREPARATIONS recorded in Part I of this series [1] yielded considerable quantities of the androst-2-enes (I; R = :O, R′ = H, β-OH, and :O), which have now been used to afford, by standard methods, a series of 11 : 17-disubstituted androstanes and some other derivatives *not* substituted at position 3. These products provide reference values for optical rotations, infrared spectra, etc., which permit the assessment of vicinal action between positions 11 and 17, uncomplicated by the presence of substituents at position 3.*

Four 11-monoketones have recently been described by the Syntex group; [2] 5α-androstan-11-one had been prepared some years earlier by Steiger and Reichstein.[3]

Infrared Spectra.—These were measured for carbon disulphide solutions.

Carbonyl bands (Table 1). In the carbonyl stretching region (1750—1700 cm.$^{-1}$) the frequencies for the reference compounds agree with those found elsewhere for compounds containing other functional groups (see, *e.g.*, the review by Jones and Herling [4]). The 11β-acetoxyl and 17-oxo-groups mask each other; the only true reference value for 11β-acetoxyl is therefore that for 5α-androstan-11β-yl acetate itself.

Results in the " finger-print " region below 1350 cm.$^{-1}$ in general agree with, and supplement, the data already available in the literature; [4-6] for the 11 : 17-disubstituted compounds it is usually possible to recognise the main bands associated with the individual functions, although the absolute positions of the bands may be somewhat altered.[11]

17-Ketones have two strong bands [2] at about 1055 and 1010 cm.$^{-1}$. 11-Ketones have two or three bands at about 1080, 1050, and 1020 cm.$^{-1}$. The 17-ketone band (~1010 cm.$^{-1}$) occurs at a significantly higher wave-number in the 9(11)-unsaturated compounds (II and IV; R = :O) than in the saturated compounds. In the keto-acetates the bands of the two functions in the 1020—1030 cm.$^{-1}$ region inevitably mask one another as do the carbonyl and the hydroxyl bands at about 1050 cm.$^{-1}$ (see Tables 1 and 3). The strong 17β-acetate

* While this paper was in press it was brought to our notice that similar work had been carried out at the Upjohn Co., Kalamazoo, Mich. (cf. Babcock, *Abs. Meeting Amer. Chem. Soc.*, April, 1956).

[1] Part I, Klyne and Ridley, *J.*, 1956, 4825.
[2] Sondheimer, Batres, and Rosenkranz, *J. Org. Chem.*, 1957, **22**, 1090.
[3] Steiger and Reichstein, *Helv. Chim. Acta*, 1937, **20**, 817.
[4] R. N. Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252.
[5] R. N. Jones, Herling, and Katzenellenbogen, *J. Amer. Chem. Soc.*, 1955, **77**, 651.
[6] R. N. Jones and Herling, *ibid.*, 1956, **78**, 1152.

TABLE 1. *Infrared spectra: carbonyl bands.*

Substituents at 17 R	11 R′	Carbonyl stretching: 17-CO	11-CO	17β-OAc	11β-OAc	Below 1350 cm.⁻¹: 17-CO	11-CO	17β-OAc	11β-OAc
5α-Androstane derivatives (III)									
H_2	:O	—	1700,[a] 1704	—	—	—	1070, 1060, 1029	—	—
:O	H_2	1745[b]	—	—	—	1055, 1010	—	—	—
H_2	H, β-OAc	—	—	—	1725	—	—	—	1240, 1214i, 1026
H, β-OAc	H_2	—	—	1730	—	—	—	1245, 1220i, 1032	—
:O	H, β-OH	1742	—	—	—	1062,[a] 1015	—	—	—
:O	H, β-OAc	1740	—	—	1728	1052, 1010	—	—	1235, 1213i
H, β-OH	:O	—	1712	—	—	—	1082, 1053,[a] 1027	—	—
H, β-OAc	:O	—	1707	1737	—	—	1077, 1040, 1025	1235, 1215i	—
:O	:O	1748	1715	—	—	1010	1082, 1022 1050	—	—
H, β-OAc	H, β-OAc	—	—	1744—1735	—	—	—	1240, 1224i, 1030	
H, β-OAc	H, β-OH	—	—	1744	—	—	—	1247, 1220i, 1035[a]	
5α-Androsta-9(11)-ene derivatives (IV)									
:O	—	1742	—	—	1059, 1022	—	—	—	—
H, β-OAc	—	—	—	1732	—	—	—	1239, 1034	
5α-Androsta-2 : 9(11)-diene derivatives (II)									
:O	—	1745	—	—	—	1061, 1025	—	—	—
H, β-OAc	—	—	—	1728	—	—	—	1235, 1032	
5α-Androst-2-ene derivatives (I)									
:O	H, β-OH	1743	—	—	—	1054,[a] 1010	—	—	—
O	:O	1740	1709	—	—	1006	1080, 1045	—	—

[a] Bands masking 1050 cm.⁻¹ region. i = inflexion.
[a] Ref. 2. [b] Rosenkranz and Zablow, *J. Amer. Chem. Soc.*, 1953, **75**, 903.

TABLE 2. *Infrared spectra: olefinic bands.*

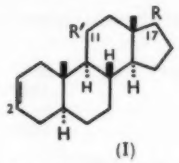
	Olefinic CH stretching	C=C stretching: Δ^2	C=C stretching: $\Delta^{9(11)}$	Olefinic CH out-of-plane bending: Δ^2	Olefinic CH out-of-plane bending: $\Delta^{9(11)}$	Ref.
2-Enes						
5α-Cholest-2-ene	3034	1653	—	664, 774	—	8
11β-Hydroxy-5α-androst-2-en-17-one	3040	1653	—	662, 770	—	1
5α-Androst-2-ene-11 : 17-dione	3040	1653	—	662, 769	—	1
5α-Androst-2-en-17-one	—	1651	—	—	—	9
9(11)-Enes						
3β-Acetoxy-5α-ergost-9(11)-ene	3045	—	1640	—	820, 840	10
24-Hydroxy-5β-chol-9(11)-ene	3042	—	1644	—	827, 852	7
Me 5β-chol-9(11)-enate	3037	—	1643	—	—	7
5α-Androst-9(11)-en-17-one	3060	—	—	—	813	—
5α-Androst-9(11)-en-17β-ol	3060	—	1630	—	810	—
5α-Androst-9(11-)en-17β-yl acetate	3060	—	—	—	814	—
2 : 9(11)-Dienes						
5α-Androsta-2 : 9(11)-dien-17-one	3040	1663	—	665—653 (d)	818	—
5α-Androsta-2 : 9(11)-dien-17β-ol	3040	1661	1638 (sh)	657 (i), 665	820	—
5α-Androsta-2:9(11)-dien-17β-yl acetate	3040	1650	—	660 (i), 648	813	—

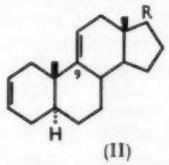
[7] Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402.
[8] Henbest, Meakins, and Wood, *J.*, 1954, 800.
[9] R. N. Jones, Humphries, Packard, and Dobriner, *J. Amer. Chem. Soc.*, 1950, **72**, 86.
[10] Crawshaw, Henbest, and E. R. H. Jones, *J.*, 1954, 731.

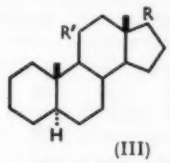
band which is normally [6] at 1247—1245 cm.$^{-1}$ is moved to 1239—1235 cm.$^{-1}$ in the 11-oxo-17β-acetate (III; R = H, β-OAc, R′ = :O) and the 9(11)-ene and 2 : 9(11)-diene 17β-acetates (IV and II; R = H, β-OAc).

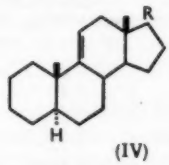
Olefinic bands (Table 2). Olefinic C:CH bands at ~3040—3060 cm.$^{-1}$ are found in the spectra of all the unsaturated compounds.

The C:C stretching bands for monounsaturated compounds show a characteristic difference between those for 2-enes (1657—1653 cm.$^{-1}$) and those for 9(11)-enes (1644—1640 cm.$^{-1}$), as found in previous work.[7,8] In the 2 : 9(11)-dienes the peak is in the 1660—1650 cm.$^{-1}$ region, with a shoulder on the smaller wave-number side in one case.


(I)


(II)


(III)


(IV)

These bands are often obscured in compounds containing ketone or acetoxyl groups;[7,9] our results confirm this.

The CH out-of-plane bending frequencies for 2-enes (disubstituted) and 9(11)-enes (trisubstituted) showed the characteristic differences indicated in previous work.[7,8] In the 2 : 9(11)-dienes both bands appeared. For 9(11)-enes the androstene derivatives show appreciable differences in the position of the ~800 cm.$^{-1}$ band from that for ergostene and cholene derivatives.[7,10]

Hydroxyl bands (Table 3). The free hydroxyl stretching band at 3645—3665 cm.$^{-1}$ is shown by all the hydroxyl compounds; in addition, the 11β-hydroxy-17-ketones, 17β-hydroxy-11-ketone, and 17β-acetoxy-11β-alcohol show evidence of hydrogen bonding (3500—3400 cm.$^{-1}$).[4]

TABLE 3. *Infrared spectra: hydroxyl bands.*

	Free OH stretching	Hydrogen-bonded OH stretching	C–OH stretching 11β-OH	17β-OH
5α-Androstan-11β-ol	3665	—	1055	—
5α-Androst-9(11)-en-17β-ol	3665	—	—	1055
5α-Androsta-2 : 9(11)-dien-17β-ol	3645	—	—	1062
5α-Androstane-11β : 17β-diol	3645	—	1052 (broad)	
17β-Acetoxy-5α-androstan-11β-ol	3660	Extensive H-bonding	*	—
11β-Hydroxy-5α-androstan-17-one	3645	Extensive H-bonding	*	—
11β-Hydroxy-5α-androst-2-en-17-one	3650	H-bonding	*	—
17β-Hydroxy-5α-androstan-11-one	3640	3500—3400	—	*

* Masked, see Table 1.

C–OH stretching bands at ~1050—1060 cm.$^{-1}$ are shown by all the hydroxy-compounds having no other substituent; masking occurs in the acetoxy-hydroxy- and hydroxy-keto-compounds, as indicated in Tables 1 and 3.

Molecular Rotations.—The molecular rotations (M_D) and differences (Δ values) for the principal compounds studied here, and for reference compounds in other series, are collected in Table 4. These values permit an assessment of vicinal action between positions 11 and 17. The principal findings in our work are as follows: (i) An 11β-hydroxyl group has little effect on functions at position 17. Acetoxyl and carbonyl groups at positions 11 and 17, or *vice versa*, show considerable vicinal action. (ii) 17-Substituents have a considerable effect on the 9(11)-double bond.

Comparison of the contributions of the 11-carbonyl group in the four monoketones prepared by Sondheimer, Batres, and Rosenkranz [2] shows some interesting effects. The Δ(C:O)-11 values are as follows: 5α-Androstane +176° (our value, +182°); 5β-androstane +140°; 5α-pregnane +129°; 5β-pregnane +105° (Ruff and Reichstein [11] found +111°); 5α-cholestane +118° (Table 4); and 5α-ergostane +120° (Table 4).

[11] Ruff and Reichstein, *Helv. Chim. Acta*, 1951, **34**, 70.

Differences between the 5α- and the 5β-series are not unexpected, but the differences of 25—45° between the C_{19} compounds of the androstane series on the one hand, and C_{21}, C_{27}, and C_{28} compounds (with a 17-side chain) on the other hand, are noteworthy.

TABLE 4. *Molecular rotations.*

Values in bold type are $[M]_D$ in $CHCl_3$; values in ordinary light type are Δ values at C-17 (*e.g.*, $[M]_D$ 17CH·OH − $[M]_D$ 17CH_3); values in italic type are Δ values at C-11 (*e.g.*, $[M]_D$ 11CO − $[M]_D$ 11CH_2).

	5α-Androstane series, No substituents at C-3							5α-Cholestane series		5α-Ergostane series	
11-Substituent	17-CH_2	17β-OH	Δ	17β-OAc	Δ	17CO	Δ	3β-OH	3β-OAc	3β-OH	3β-OAc
None	+2° [a]	+29° [a]	+27°	+6° [a]	+14°	+260° [b]	+258°	+89° [c]	+60° [c]	+64° [d]	+27° [d]
11β-OH	**+47**	**+84**	+37	**+23**	−24	**+288**	+241	—	—	**+118** [d]	**+115** [e]
	+45	*+55*		*+17*		*+28*				*+54*	*+88*
11β-OAc	**+112**	—		**+89**	+23	**+238**	+126	—	—	**+208** [d]	**+155** [d]
	+110			*+83*		*−22*				*+144*	*+128*
11-Oxo	**+184** [a]	**+162**	−22	**+58**	−126	**+389**	+205	—	**+178** [f]	—	**+147** [g]
	+182	*+133*		*+52*		*+129*			*+118*		*+120*
9(11)-Ene	—	**+11**		**−16**		**+364**		**+104** [h]	**+96** [h]	**+116** [g]	**+75** [g]
	—	*−18*		*−22*		*+104*		*+15*	*+36*	*+42*	*+58*
9(11)-Ene, with 2-ene	—	**+89**		**+42**		**+473**		—	—	—	—

[a] Ref. 2, +178°. [b] Unpublished values from Mr. P. M. Jones of this laboratory. [c] Rosenkranz, Kaufmann, and Romo, *J. Amer. Chem. Soc.*, 1949, **71**, 3689. [d] Barton and Cox, *J.*, 1948, 783. [e] Crawshaw, Henbest, E. R. H. Jones, and Wagland, *J.*, 1955, 3420. [f] Ref. 10. [g] Heusser, Heusler, Eichenberger, Honegger, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 295. [h] Heusser, Eichenberger, Kurath, Dillenbach, and Jeger, *ibid.*, 1951, **34**, 2106. [i] Fieser and Huang, *J. Amer. Chem. Soc.*, 1953, **75**, 5356.

EXPERIMENTAL

M. p.s were determined on a hot stage and are corrected. Optical rotations were determined for chloroform solutions (*c* 0·7—1·3%) and the sodium D line, in a 1 dm. micro-tube, at room temperature (18—25°). Analytical samples were dried at 80°, or at least 20° below the m. p.

Infrared spectra were determined for carbon disulphide solutions with a Perkin-Elmer model 21 double-beam spectrophotometer, fitted with a sodium chloride prism, by Dr. A. A. Wagland, Roche Products Ltd., Welwyn Garden City.

Ultraviolet spectra were determined with a Unicam SP 500 spectrophotometer by Dr. G. W. Wood, Hatfield Technical College.

"Working up in the usual manner" implies washing the organic layer with water, 2N-sulphuric acid, water, saturated sodium hydrogen carbonate solution, and then water until washings are neutral.

Light petroleum refers to the fraction of b. p. 60—80°.

5α-Androsta-2 : 9(11)-dien-17-one (II; R = :O).—Redistilled phosphorus oxychloride (1 c.c.) was added dropwise to a solution of 11β-hydroxy-5α-androst-2-en-17-one (I; R = :O, R′ = H, β-OH) (200 mg.) in dry pyridine (4 c.c.) with external cooling. The solution was kept at room temperature overnight, and the steroid isolated by means of ether in the usual manner. The solid product (168 mg.) was chromatographed on alumina (6 g.). Elution with light petroleum and light petroleum–benzene (9 : 1) yielded material of m. p. 124—129° (91 mg.), crystallizing from *n*-pentane to yield the *dienone*, m. p. 131—133° (depressed m. p. when admixed with starting material), $[\alpha]_D$ + 173° (Found: C, 84·35; H, 9·7; $C_{19}H_{26}O$ requires C, 84·4; H, 9·7%). ε 6012, 4202, 1748, 480, and 166 at 2000, 2050, 2100, 2150, and 2200 Å, respectively.

Further elution of the column with light petroleum–benzene (1 : 3) and benzene gave unchanged starting material, crystallizing from acetone as needles, m. p. and mixed m. p. 129—133°.

5α-Androsta-2 : 9(11)-dien-17β-ol (II; R = H, β-OH).— A solution of lithium aluminium hydride (100 mg.) and 5α-androsta-2 : 9(11)-dien-17-one (II; R = O) (128 mg.) in dry ether (10 c.c.) was kept at room temperature overnight. Ethyl acetate and then water were added to decompose the excess of reagent, aqueous tartaric acid solution added, and the steroid isolated

with ether in the usual manner to give a solid (123 mg.). Chromatography on alumina (4 g.), elution with light petroleum–benzene (1 : 1 and 1 : 3) and benzene, and crystallization from light petroleum yielded *5α-androsta-2 : 9(11)-dien-17β-ol*, m. p. 163—164° (with previous sublimation to give needles), $[\alpha]_D$ +33° (Found: C, 83·85; H, 10·4. $C_{19}H_{28}O$ requires C, 83·75; H, 10·35%).

The *acetate*, prepared with acetic anhydride and pyridine in the usual way and recrystallized from methanol, had m. p. 79—81°, with an abrupt change after several crystallizations to 97—99°, $[\alpha]_D$ + 13° (Found: C, 80·5; H, 9·55. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

11β-Hydroxy-5α-androstan-17-one (III; R = :O, R′ = H, β-OH).—A solution of 11β-hydroxy-5α-androst-2-en-17-one (I) (500 mg.) in ethyl acetate (60 c.c.) containing prereduced Adams catalyst (70 mg.) was shaken under slight positive pressure in hydrogen. Uptake ceased (4 min.) after the addition of 1 mol. of hydrogen. Removal of the catalyst and evaporation of the solvent yielded a solid which crystallized from acetone–pentane, to give the *hydroxy-ketone*, m. p. 178—179°, $[\alpha]_D$ +78° (Found: C, 78·3; H, 10·35. $C_{19}H_{30}O_2$ requires C, 78·55; H, 10·4%).

This hydroxy-ketone (150 mg.) was heated in dimethylaniline (3·6 c.c.), redistilled acetyl chloride (1·8 c.c.), and chloroform (5·4 c.c.) for 7·5 hr., then kept at room temperature overnight. After the addition of iced water, the steroid was worked up in ether in the usual manner, yielding a yellow gummy solid. Chromatography on alumina (6 g.) and elution with light petroleum–benzene (4 : 1 to 1 : 1) gave the *11β-acetate*, prisms (from methyl alcohol), m. p. 116·5—118°, $[\alpha]_D$ +71° (Found: C, 75·7; H, 9·65. $C_{21}H_{32}O_3$ requires C, 75·8; H, 9·7%).

5α-Androst-9(11)-en-17-one (IV; R = :O).—Phosphorus oxychloride (1 c.c.) and 11β-hydroxy-5α-androstan-17-one (200 mg.) in pyridine (4 c.c.) gave, as above, a product which was chromatographed on alumina (6 g.); elution with light petroleum–benzene (9 : 1 and 4 : 1) gave *5α-androst-9(11)-en-17-one* (74 mg.), plates (from methyl alcohol), m. p. 133—134° (with some previous softening and sublimation), $[\alpha]_D$ +134° (Found: C, 83·5; H, 10·3. $C_{19}H_{28}O$ requires C, 83·75; H, 10·35%), ε 5340, 3410, 1233, and 86 at 2000, 2050, 2100, and 2150 Å, respectively.

5α-Androst-9(11)-en-17β-ol (IV; R = H, β-OH).—The monounsaturated ketone (IV; R = :O) (179 mg.) was reduced with lithium aluminium hydride in ether as above. Chromatography on alumina (6 g.) and elution with light petroleum–benzene (1 : 1 to 1 : 3) gave crude *5α-androst-9(11)-en-17β-ol*, needles (from light petroleum), m. p. 160·5—162° (subliming as needles and laths), $[\alpha]_D$ +4° (Found: C, 83·45; H, 11·0. $C_{19}H_{30}O$ requires C, 83·15; H, 11·05%). This alcohol (54 mg.) with pyridine and acetic anhydride in the usual manner gave the acetate, m. p. 66·5—69·5° (from methanol), $[\alpha]_D$ −5°.

5α-Androstane-11 : 17-dione (III; R = R′ = :O).—(a) *By hydrogenation of 5α-androst-2-ene-11 : 17-dione.* A solution of the androstenedione (413 mg.) in ethyl acetate (45 c.c.), hydrogenated over Adams catalyst as above (15 min.), gave a solid, which was filtered through alumina (12 g.) in light petroleum–benzene (1 : 1), further material being obtained by elution with the same solvents (3 : 1) and benzene. Crystallization from light petroleum and a trace of acetone gave *5α-androstane-11 : 17-dione* as plates, m. p. 126—127·5° (200 mg.), and a second crop (86 mg.), m. p. 125—127°, $[\alpha]_D$ +135° (Found: C, 78·8; H, 9·75. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%). This compound gave no colour with tetranitromethane.

(b) *Chromic acid oxidation of 5α-androstane-11β : 17β-diol.* 8N-Chromic acid (aqueous) [7] was added dropwise to a solution of the diol (18 mg.) in acetone (5 c.c.), until excess of reagent was present. After a further minute's shaking water was added and the steroid worked up in ether in the usual manner. The solid product (16 mg.) was chromatographed on alumina (1 g.). Elution with light petroleum–benzene (3 : 1 and 1 : 1) and crystallization from methanol gave plates, m. p. 125—128°, undepressed on admixture with material prepared by method (a).

(c) *Chromic acid oxidation of 11β-hydroxy-5α-androstan-17-one.* The hydroxy-ketone was oxidized as in method (b); the product crystallized from *n*-pentane to give plates, m. p. and mixed m. p. 126—129°.

5α-Androstane-11β : 17β-diol (III; R = R′ = H, β-OH).—(a) *By hydrogenation.* A solution of 5α-androst-2-ene-11 : 17-dione (500 mg.) in acetic acid (55 c.c.) was hydrogenated using prereduced Adams catalyst (70 mg.). One mol. of hydrogen was absorbed in 6 min., 2 mols. in 30 min., and uptake ceased after 100 min. Removal of the catalyst and evaporation to dryness yielded a solid (512 mg.), m. p. 151—153° with a partial change to fine needles. Slow crystallization from light petroleum gave *5α-androstane-11β : 17β-diol* as hair-like needles (485 mg.), m. p. 156—158° (with sublimation to larger needles). The infrared spectrum of this

product showed a small peak at 1717 cm.$^{-1}$ (11-CO); chromatography and crystallization of the product eluted with benzene–ether (19 : 1 to 1 : 1) gave needles, m. p. 160—162°, $[\alpha]_D$ +29° (no infrared ketone peak) (Found: C, 78·25; H, 10·85. $C_{19}H_{32}O_2$ requires C, 78·0; H, 11·05%).

(b) *By reduction with lithium aluminium hydride.* Lithium aluminium hydride (50 mg.) was added to a solution of 5α-androstane-11 : 17-dione (40 mg.) in dry ether (1 c.c.), and the whole kept at room temperature overnight. Working up in ether gave a gelatinous solid (42 mg.). Chromatography on alumina (1 g.), elution with benzene–ether (19 : 1 to 1 : 1), and crystallization from light petroleum gave the diol as fibrous needles, m. p. and mixed m. p. 161—163° (with sublimation), $[\alpha]_D$ +29°.

Acetylation with pyridine and acetic anhydride at room temperature overnight gave *5α-androstane-11β : 17β-diol 17-monoacetate*, crystallizing from methanol as needles, m. p. 138—139°, $[\alpha]_D$ +7° (Found: C, 75·0; H, 10·25. $C_{21}H_{34}O_3$ requires C, 75·4; H, 10·25%).

11β : 17β-Diacetoxy-5α-androstane.—The preceding diol (150 mg.) was acetylated with acetyl chloride in dimethylaniline and chloroform as for the 11β-hydroxy-17-ketone. Chromatography of the product on alumina (6 g.) and elution with light petroleum–benzene (19 : 1 to 1 : 3) yielded a gummy solid (165 mg.), which gave the *diacetate*, m. p. 122—124° (113 mg.), on trituration with methanol. Further crystallization gave material of m. p. 123—125°, $[\alpha]_D$ +24° (Found: C, 73·0; H, 9·7. $C_{23}H_{36}O_4$ requires C, 73·4; H, 9·65%).

17β-Hydroxy-5α-androstan-11-one (III; R = H, β-OH, R′ = :O).—Sodium borohydride (18 mg.) was added to a solution of 5α-androstane-11 : 17-dione (286 mg.) in methanol (60 c.c.) at 0°, and the solution kept at this temperature for 1 hr. A few drops of acetic acid were added to decompose the excess of reagent. Working up in the usual way in ether gave a colourless solid (287 mg.). Chromatography on alumina (10 g.) and elution with benzene–ether (19 : 1 and 9 : 1) gave material, m. p. 148—151° (154 mg.) (with previous sublimation to needles). Crystallization from acetone–light petroleum then gave *17β-hydroxy-5α-androstan-11-one*, needles, m. p. 149—151·5° (with previous sublimation), $[\alpha]_D$ +56° (Found: C, 78·4; H, 10·25. $C_{19}H_{30}O_2$ requires C, 78·55; H, 10·4%). This material (50 mg.) with acetic anhydride and pyridine gave the *17β-acetate*, laths (from methanol), m. p. 106—108°, $[\alpha]_D$ +17° (Found: C, 75·95; H, 9·45. $C_{21}H_{32}O_3$ requires C, 75·8; H, 9·7%).

5α-Androstan-11β-ol (III; R = H_2, R′ = H, β-OH).—Potassium hydroxide (900 mg.), 100% hydrazine hydrate (1 c.c.), and 5α-androstane-11 : 17-dione (317 mg.) in triethylene glycol (45 c.c.) were heated under reflux for 30 min. The solution was then heated at 200° for 2 hr. Water and 2N-sulphuric acid were added to the cooled solution; extraction with ether and working up in the usual manner gave a brown gum (287 mg.) which was filtered in pentane through alumina (9 g.), to yield a gum (223 mg.). Reduction of this with lithium aluminium hydride in the usual manner gave a gummy solid (219 mg.), which on chromatography on alumina (20 g.) and elution with light petroleum gave *5α-androstan-11β-ol* (144 mg.), plates (from light petroleum), m. p. 89—91°, $[\alpha]_D$ +17° (Found: C, 82·25; H, 11·7. $C_{19}H_{32}O$ requires C, 82·5; H, 11·7%).

Acetylation of this alcohol (123 mg.) with acetyl chloride, dimethylaniline, and chloroform gave the *acetate* as a gum which was purified by chromatography and distillation *in vacuo*. It then had $[\alpha]_D$ +35° (Found: C, 80·75; H, 11·0. $C_{21}H_{34}O_2$ requires C, 81·0; H, 10·75%). After a time part of this material solidified, enabling the product to be crystallized from methanol to yield prisms, m. p. 70—72°.

5α-Androstan-11-one (III; R = H_2, R′ = :O).—8N-Chromic acid was added dropwise to a solution of 5α-androstan-11β-ol (160 mg.) in acetone (5 c.c.) until an excess was present; after the addition of water the steroid was worked up in ether in the usual manner, to yield the ketone as needles (from methanol), m. p. 49—51·5°, $[\alpha]_D$ +68°.

Sondheimer, Batres, and Rosenkranz [2] give m. p. 49—50°, $[\alpha]_D$ +65°, for a sample obtained by high-vacuum distillation; Steiger and Reichstein [3] give m. p. 50—52°.

We are greatly indebted to Messrs. Glaxo Laboratories Ltd., Greenford, Middlesex, for a generous gift of starting materials; to Dr. A. A. Wagland and Messrs. Roche Products Ltd., Welwyn Garden City, Herts., for the infrared spectra; and to Dr. G. W. Wood, Hatfield Technical College, Hatfield, Herts., for the ultraviolet spectra.

Medical Research Council Steroid Reference Collection,
Postgraduate Medical School,
Ducane Road, London, W.12.

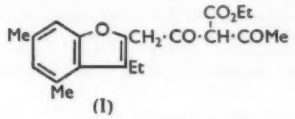
[*Received, June 23rd,* 1958.]

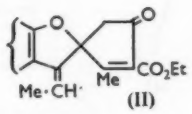
918. *Spirans. Part II.* The Preparation and Ozonolysis of Derivatives of 3-Ethylidenegris-2′-ene. Anomalous Enolisation in β-Oxo-esters.*

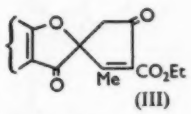
By F. M. Dean, Thomas Francis, and Kamchorn Manunapichu.

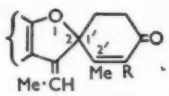
The cyclisation of appropriately substituted 3-alkylbenzofurans has been extended from the synthesis of *cyclo*pent-2′-ene-1′-*spiro*-2-coumarans to that of 3-alkylidenegris-2′-enes, ozonolysis of which is abnormal and gives derivatives (V) of 2 : 3 : 4 : 4a : 6 : 6a-hexahydro-1*H*-5 : 11-dioxadibenzo[*a*,*d*]-pentalene. The properties of certain β-oxo-esters in this series are interpreted in terms of the non-classical enol R·CO·C:C(OH)·OR.

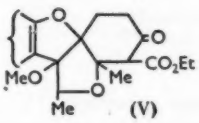
Previously,[1] *spiro*coumarans of type (II) were obtained by cyclisation of diketo-esters of type (I) and oxidised by ozone to *spiro*coumaranones (III). In extension, the gris-2′-ene (IV) has been similarly synthesised but found to yield with ozone, not the expected grisenone related to griseofulvin,[2] but the condensed difuranoid β-oxo-ester (V) as an enol of unusual character.

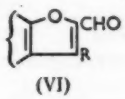

(I)

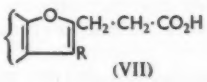

(II)

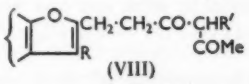

(III)

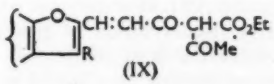

(IV)

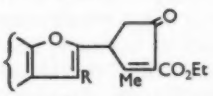

(V)

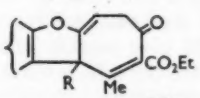

(VI)

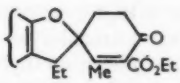

(VII)


(VIII)


(IX)


(X)


(XI)


(XII)

The acrylic acids resulting from interaction of the aldehydes (VI; R = Me or Et) with malonic acid gave on hydrogenation the β-(benzofuryl)propionic acids (VII; R = Me or Et), the acid chlorides of which with methoxymagnesio-derivatives of the appropriate acetoacetates or of acetylacetone gave crude diketones (VIII; R = Me or Et, R′ = CO_2Me, CO_2Et, or Ac), converted by sulphuric acid into *spiro*coumarans of type (IV). Although β-(3 : 4 : 6-trimethylbenzofur-2-yl)acrylic acid supplied a crystalline dioxo-ester (IX) with properties typical of β-dicarbonyl compounds, this ester failed to give a spiran as condensation product, presumably because the dienone type of structure which would have resulted is itself labile to acids.[3] Because ozonolysis of the ethylidenecoumaran (II) to the coumaranone (III) was essential in the proof [1] of the spiran nature of these compounds but took a different course in the present series, formulæ of types (X) and (XI) could not be rejected by analogy only. However, the infrared absorption spectra of the cyclisation products always possessed bands near 1680 cm.$^{-1}$ consistent with the *cyclo*hexenone-carbonyl group of structure (IV) but not with the *cyclo*pentenone-carbonyl group of (X);

* Part I, *J.*, 1957, 3112 (with the series title, "Spirocyclic Compounds").

[1] Dean, Halewood, Mongkolsuk, Robertson, and Whalley, *J.*, 1953, 1250.
[2] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3977.
[3] Arkley, Dean, Robertson, and Sidisunthorn, *J.*, 1956, 2322 and references cited therein.

XUM

and under conditions in which a furan double bond, as in (X), is invariably resistant, hydrogenation of the cyclisation product (IV; R = CO_2Et) readily gave a dihydro-derivative (XII) retaining this carbonyl absorption. The corresponding ultraviolet spectra (Fig. 1) paralleled those in the established series and showed that the dihydro-derivative lacked an absorption band of $\lambda_{max.}$ 242 mμ (log ε 4·15), clearly indicating loss of a styrene chromophore of $\lambda_{max.}$ 244 mμ (log ε 4·1): this evidence eliminated structures of type (XI).

The spiran esters (IV) gave the usual carbonyl derivatives, and one (IV; R = CO_2Et) was hydrolysed with difficulty to the corresponding acid (IV; R = CO_2H), decarboxylation of which was unsatisfactory but gave the grisenone (IV; R = H) with the appropriate

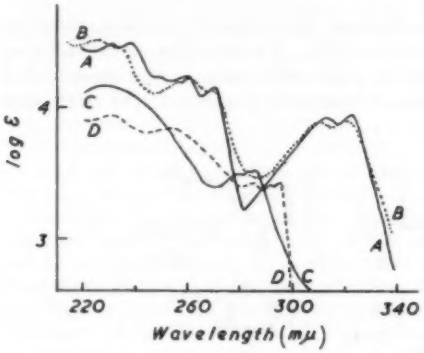
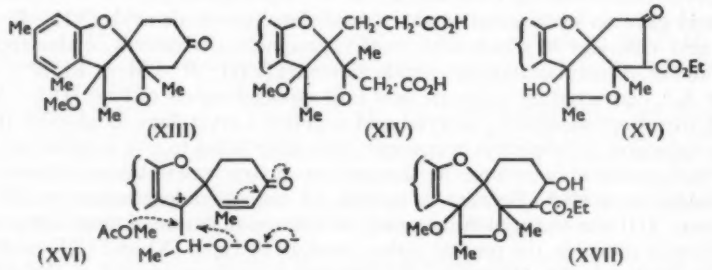


FIG. 1. *Ultraviolet spectra of*: *A*, *ethyl* 3-*ethylidene*-4 : 6 : 2′-*trimethyl*-4′-*oxogris*-2′-*ene*-3′-*carboxylate* (IV; R = CO_2Et); *B*, *ethyl* 4 : 6 : 2′-*trimethyl*-3-*methylene*-4′-*oxocyclopent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylate* (II); *C*, *dihydro-derivative* (XII) *of* (*A*); *and D*, *ozonolysis product* (V) *of* (A) (*all in alcohol*).

spectroscopic properties. The same grisenone (IV; R = H) resulted when its acetyl derivative (IV; R = Ac) was hydrolysed by acid, and also when the diketone obtained by selective deacetylation of triketone (VIII; R = Et, R′ = Ac) with sodium methoxide was cyclised with sulphuric acid.

No conditions were found in which ozonolysis of the 3-methylenegrisenone (IV; R = CO_2Et; with $=CH_2$ for =CHMe) in the usual solvents, or of the 3-ethylidenegrisenones (IV) in carbon tetrachloride, would give volatile aldehydes or tractable residues. In contrast, ozonolysis in methyl acetate (for which ethyl acetate could not be substituted) smoothly converted the 3-ethylidenegrisenone (IV; R = CO_2Et) into a product to which we ascribe structure (V). No peroxidic materials were detected in the reaction mixture.



The ozonolysis product (V) gave analytical data consistent with the uptake of one oxygen atom and the elements of methanol. Since the compound was devoid of hydroxyl absorption near 3 μ, was stable to severe drying, and retained the methoxyl group during degradation, the presence of methoxyl was clearly not due to solvation. The product was obviously a β-oxo-ester because of its solubility in alkali, its intense ferric reaction, and its dual hydrolysis in warm alkali to ketonic (XIII) and acidic (XIV) products. The grisanone

(XIII) had the requisite carbonyl band at 1717 cm.$^{-1}$ but was transparent near 3 μ, gave a 2 : 4-dinitrophenylhydrazone and a positive Zimmermann reaction, possessed an ultraviolet spectrum typical of a simple coumaran (Fig. 2), and was also obtained directly by ozonolysis of the appropriate grisenone (IV; R = H) in methyl acetate. The dibasic acid (XIV) had almost the same ultraviolet spectrum as the ketone (XIII), gave a dimethyl ester with selective absorption at 1742 cm.$^{-1}$ (saturated ester) but none near 3 μ, and had pK_a 4·85 (one inflection) typical of propionic acids.

FIG. 2. *Ultraviolet spectra of: A, ketone* (XIII); *B, diacid* (XIV); *and C,* 1 : 2 : 3 : 4 : 10 : 11-*hexahydro*-6 : 11-*dimethyldibenzofuran*-2-*one*[3] (*all in alcohol*).

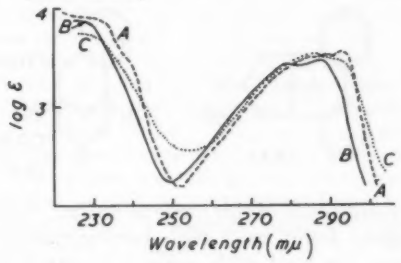
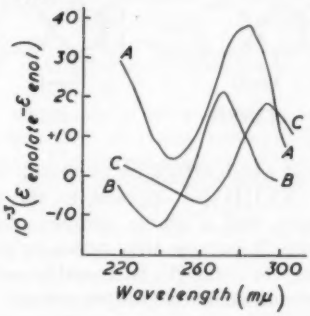


FIG. 3. Δε *curves for: A, ozonolysis product* (V); *B, ethyl acetoacetate; and C, acetylacetone. Spectra were obtained from* 10^{-4}M-*solutions in neutral alcohol and in* 0·01N-*alcoholic sodium hydroxide. The data for B and C in neutral alcohol were amended to give values approximating to those for* 100% *enolisation.*



The ultraviolet spectrum of the β-oxo-ester (V) was difficult to dissect into its components, but by subtraction[4] the spectra in neutral and alkaline alcohol gave a curve characteristic of the enolic system only, comparable to those obtained from typical β-dicarbonyl compounds (Fig. 3).

Because the ozonolysis product (V) has hydrogen at the 3′-position,* either the methoxyl group or the oxygen atom must be placed at the 2′-position, but as the grisenone (IV) does not add methanol (except during ozonolysis) and the methoxyl group survives alkaline and acid fission it is the oxygen atom which is located at the 2′-position since its stability in a position β to carbonyl is then explicable on stereochemical grounds (a similar example is discussed in ref. 3). In conjunction with the relative reactivity of the exocyclic double bond of the grisenone (IV) [compounds of type (XII) resist ozone] and the strain involved in 4-membered rings, these facts lead uniquely to structure (V) for the ozonolysis product.

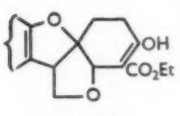
The stability of the benzyl ether system to acids and hydrogenolysis [as in the diacid (XIV)] conforms with a structure (V) because a flat carbonium centre at the 3-position would be highly strained and because access of catalysts to the same site would be considerably hindered. Finally, structure (V) is strongly supported by the oxidation of the authentic *spiro*pentenone (II) with osmium tetroxide which gave the β-oxo-ester (XV) instead of a glycol.

That the 2′ : 3′- and the ethylidene double bond are more divergent in the *cyclo*pentenone (II) than in the *cyclo*hexenone (IV) may account for their different modes of ozonolysis. The ozonolysis could not be simulated by peracids in the presence of methanol, so both double bonds might be involved in ozonolysis as represented in (XVI).

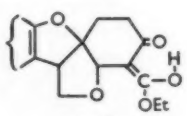
* Grisan numbering (cf. IV).[3]

[4] Aulin-Erdtman, *Chem. and Ind.*, 1955, 581.

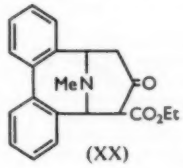
Compound (V) has physical and chemical properties more easily explained in terms of a non-classical enol of type (XIX) than in terms of a conventional enol of type (XVIII). In the crystalline state or in solution (0·05M in chloroform) the β-oxo-ester (V) has no carbonyl absorption above 1630 cm.$^{-1}$ (and no hydroxyl absorption near 3 μ), thus contrasting with the majority of 2-oxo*cyclo*hexanecarboxylates which also show frequencies characteristic of the non-enolised ester and carbonyl groups.[5] Supercooled melts of the β-oxo-ester (V) do have prominent absorption frequencies at 1757 (ester) and 1727 cm.$^{-1}$ (C:O), from which it follows that the β-oxo-ester is normally completely enolised. The observed frequency at 1630 cm.$^{-1}$ is ~25 cm.$^{-1}$ lower than expected for a chelated ester,[5] but is consistent with a chelated carbonyl group as in (XIX). In general, hydrolysis of 2-oxo-*cyclo*alkanecarboxylic esters by dilute alkali results chiefly in loss of the ester group and production of the *cyclo*alkanone: instead, the ester (V) is hydrolysed preponderantly to the diacid (XIV), a result which follows from the retention in enol form (XIX) of the carbonyl



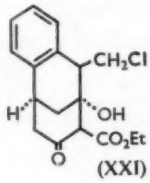
(XVIII)



(XIX)



(XX)



(XXI)

group at which attack by hydroxide ion is a prerequisite of this mode of fission. Whereas enols (XVIII) (as opposed to the non-enolised form) react with borohydrides giving hydrogen and a stable complex regenerating the enol with acids (*e.g.*, ethyl β-oxoglutarate [6]), because they no longer possess a carbonyl group which can be attacked by the reagent, the ester (V) is smoothly reduced to the β-hydroxy-ester (XVII), indicating that the ketonic carbonyl group is intact.

Although β-oxo-esters enolise at the carbonyl group because this avoids loss of some carboxyl resonance, the energy difference between enols (XVIII) and (XIX) cannot be very large because these merely represent different ways in which two hydroxyl groups can cross-conjugate with one carbonyl group so that a steric effect might sometimes favour the non-classical enol (XIX). The strain produced by introduction of a double bond into the *cyclo*hexane ring as in (XVIII) is not in itself enough to prevent this type of enolisation, but models suggest that, in conjunction with the constraints applied by the 5-membered rings, introduction of a short and rigid double bond would produce a nearly flat *cyclo*hexene ring. On the other hand, enolisation of type (XIX) permits the 6-membered ring to attain closely the favoured chair conformation * provided that a small angle of twist (~20°) between the exocyclic double bonds is allowed. On general grounds [7] this angle seems small enough to avoid appreciable loss of resonance energy in the chelated system. Further facts consistent with the view that the system resists introduction of an endocyclic double bond (or a similar source of rigidity) are that the β-hydroxy-ester (XVII) is not readily dehydrated, and that the oxime of the β-oxo-ester (V) could not be converted into an *iso*oxazolone.

These considerations can be extended, *e.g.*, to compounds (XX) [8] and (XXI).[9] It is significant that these compounds are completely enolised and have no carbonyl absorption above ~1620 cm.$^{-1}$, behaviour which we now regard as typical of a non-classical enol.

* That a boat conformation might be preferred in some compounds of this type does not affect the present argument.

[5] Leonard, Gutowsky, Middleton, and Petersen, *J. Amer. Chem. Soc.*, 1952, **74**, 4070.
[6] Personal communication from Dr. D. A. H. Taylor.
[7] Braude, "Determination of Organic Structures by Physical Methods," ed. Braude and Nachod, Academic Press, New York.
[8] Chapman and Meinwald, *J. Org. Chem.*, 1958, **23**, 162.
[9] Wenkert and Stevens, *J. Amer. Chem. Soc.*, 1956, **78**, 5627.

XUM

Further comment is reserved until determination of the precise stereochemistry of these systems is complete.

Experimental

Ultraviolet spectra were determined for alcohol solutions by means of a Unicam S.P. 500 Spectrophotometer. Infrared spectra were determined on Nujol mulls (unless otherwise stated) by means of Grubb-Parsons and Perkin-Elmer Model 21 double-beam spectrophotometers.

Unless qualified, light petroleum refers to the fraction b. p. 60—80°.

β-(*3-Ethyl-4 : 6-dimethylbenzofur-2-yl*)*propionic Acid* (VII; R = Et).—Malonic acid (50 g.) and 3-ethyl-2-formyl-4 : 6-dimethylbenzofuran [1] (VI; R = Et), kept at 100° in pyridine (150 ml.) containing piperidine (0·5 ml.) for 3 hr. and then cooled, gave β-(*3-ethyl-4 : 6-dimethylbenzofur-2-yl*)*acrylic acid* in pale yellow prisms (45 g.) which, when recrystallised from a large volume of dioxan, had m. p. 252° (decomp.), $\lambda_{max.}$ 245, 330 mμ (log ε 3·84, 4·38) (Found: C, 73·3; H, 6·6. $C_{15}H_{16}O_3$ requires C, 73·7; H, 6·6%), and, in methanolic suspension, gave with ethereal diazomethane the *methyl ester* forming needles, m. p. 74°, from aqueous methanol (Found: C, 74·1; H, 7·4; OMe, 11·8. $C_{15}H_{15}O_3$·OMe requires C, 74·4; H, 7·0; OMe, 12·0%). Hydrogenation of this ester (5 g.) in methanol (200 ml.) containing 5% palladium–charcoal (1 g.) furnished *methyl* β-(*3-ethyl-4 : 6-dimethylbenzofur-2-yl*)*propionate*, b. p. 210°/0·2 mm., as needles, m. p. 33° (Found: C, 73·8; H, 7·5; OMe, 12·0. $C_{15}H_{17}O_3$·OMe requires C, 73·8; H, 7·7; OMe, 11·9%).

Hydrogenation of the acrylic acid was hampered by insolubility of the acid and its sodium salt. The acrylic acid (20 g.) in 0·2N-sodium hydroxide (700 ml.) was hydrogenated at 100°/75 atm. for 6 hr. in the presence of Raney nickel (5 g.). The filtered solution was acidified, liberating β-(*3-ethyl-4 : 6-dimethylbenzofur-2-yl*)*propionic acid* which separated from alcohol–light petroleum in needles (18 g.), m. p. 113° (Found: C, 73·6; H, 7·5. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%), and with diazomethane gave the methyl ester, m. p. and mixed m. p. 33°. Attempts to crystallise the propionic acid from alcohol sometimes gave the *ethyl ester*, b. p. 158°/1·5 mm. (Found: C, 74·8; H, 8·1. $C_{17}H_{22}O_3$ requires C, 74·4; H, 8·0%).

β-(*3 : 4 : 6-Trimethylbenzofur-2-yl*)*propionic acid* (VII; R = Me).—As described for the 3-ethyl homologue, 2-formyl-3 : 4 : 6-trimethylbenzofuran (VI; R = Me) gave β-(*3 : 4 : 6-trimethylbenzofur-2-yl*)*acrylic acid*, pale yellow needles, m. p. 259° (from alcohol), $\lambda_{max.}$ 247, 255, 335 mμ (log ε 3·79, 3·79, 4·49), having carboxyl absorption at 1701 cm.$^{-1}$ (Found: C, 72·7; H, 6·1. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%). The *methyl ester* (prepared by diazomethane) crystallised from methanol in yellow prisms, m. p. 106° (Found: C, 73·5; H, 6·7; OMe, 12·9. $C_{14}H_{13}O_2$·OMe requires C, 73·7; H, 6·6; OMe, 12·7%). Hydrogenation of this acrylic acid as for the homologue, and purification of the product from aqueous alcohol, furnished β-(*3 : 4 : 6-trimethylbenzofur-2-yl*)*propionic acid*, needles, m. p. 131°, $\lambda_{max.}$ 256, 292 mμ (log ε 4·15, 3·39), with carboxyl absorption at 1717 cm.$^{-1}$ (Found: C, 72·5; H, 7·1. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%). The *methyl ester* (prepared by diazomethane) crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 36—37° (Found: C, 73·4; H, 7·6; OMe, 12·8. $C_{14}H_{15}O_2$·OMe requires C, 73·1; H, 7·4; OMe, 12·6%), also obtainable by hydrogenation (palladium–charcoal) of the above methyl acrylate.

Ethyl 2-Acetyl-3-oxo-5-(*3 : 4 : 6-trimethylbenzofur-2-yl*)*pent-4-enoate* (IX).—On treatment with phosphorus pentachloride (2 g.) in chloroform (20 ml.) at room temperature for ½ hr. and then at the b. p. for ½ hr., β-(*3 : 4 :* 6-trimethylbenzofur-2-yl)acrylic acid (2 g.) gave the acid chloride as an oil which was purified by distillation of the benzene solution and holding of the residue in a vacuum at 50° for ½ hr. Reaction of this oil in ether (100 ml.) with the methoxymagnesio-derivative (dried *in vacuo* at 50° for ½ hr.) of acetoacetic ester (1·15 ml.), also in ether (100 ml.), at the b. p. for 2 hr. gave a sticky complex from which an excess of dilute acetic acid liberated a crude diketone which crystallised from alcohol, giving the *pentenoate* in yellow needles (1·9 g.), m. p. 125°, soluble in dilute aqueous sodium hydroxide, having a red-brown ferric reaction, and giving a red solution in sulphuric acid that became violet when warmed (Found: C, 69·9; H, 6·4; OEt, 13·1. $C_{18}H_{17}O_4$·OEt requires C, 70·2; H, 6·5; OEt, 12·5%).

Ethyl 3-Ethylidene-4 : 6 : 2′-trimethyl-4′-oxogris-2′-ene-3′-carboxylate (IV; R = CO_2Et).—Prepared as in the previous example the acid chloride from β-(3-ethyl-4 : 6-dimethylbenzofur-2-yl)propionic acid (2 g.) reacted with the methoxymagnesio-derivative of acetoacetic ester (1·15 ml.), giving a crude diketo-ester (VIII; R = Et, R′ = CO_2Et) which was partially

purified by extraction of a solution in ether by aqueous sodium hydrogen carbonate and gave a red ferric reaction. Attempts to cyclise this oil with sulphuric acid, polyphosphoric acid, or benzenesulphonic acid were unsuccessful, but when dissolved in sulphuric acid monohydrate (10 ml.) the oil gave after 2 days at −2° a red mass from which the crude cyclisation product was obtained by addition of ice. When isolated with ether, washed with 2N-sodium hydroxide and then water, dried (Na_2SO_4), and recovered by evaporation of the solvent, the product could be crystallised from alcohol or light petroleum, affording *ethyl* 3-*ethylidene*-4 : 6 : 2′-*trimethyl*-4′-*oxogris*-2′-*ene*-3′-*carboxylate* in faintly yellow needles or prisms (1·2 g.), m. p. 142° (Found: C, 74·4; H, 7·1; OEt, 13·6. $C_{19}H_{19}O_3$·OEt requires C, 74·1; H, 7·1; OEt, 13·2%), with infrared absorption at 1681 (unsaturated C:O) and 1721 cm.$^{-1}$ (ester). The *dinitrophenylhydrazone* formed red needles, m. p. 233° (decomp.), from alcohol (Found: C, 62·1; H, 5·3; N, 10·7. $C_{27}H_{28}O_7N_4$ requires C, 62·3; H, 5·4; N, 10·8%), and the *oxime* (best prepared at 80°) formed prisms, m. p. 172°, from benzene–light petroleum (Found: C, 71·0; H, 7·3; N, 4·0; OEt, 12·3. $C_{19}H_{20}O_3N$·OEt requires C, 71·0; H, 7·1; N, 3·9; OEt, 12·7%).

In preliminary experiments hydrolysis of this ethyl oxogrisene-3′-carboxylate with sulphuric acid at various dilutions, with constant-boiling hydrobromic acid or hydrobromic acid in acetic acid, and with hydrochloric acid in acetic acid, gave intractable products. When the ethyl ester (0·5 g.) in boiling alcohol was heated for ½ hr. with 2N-sodium hydroxide (3 ml.), and the sticky product was liberated from the cooled and diluted solution by hydrochloric acid, purification of this product by extraction into ether and thence into aqueous sodium hydrogen carbonate followed by crystallisation from aqueous methanol afforded 3-*ethylidene*-4 : 6 : 2′-*trimethyl*-4′-*oxogris*-2′-*ene*-3′-*carboxylic acid hydrate* in yellow plates (0·2 g.), m. p. 174° (Found: C, 69·1; H, 6·5. $C_{19}H_{20}O_4,H_2O$ requires C, 69·1; H, 6·7%), with infrared bands at 3400 (OH), 1708 (CO_2H), and 1650 cm.$^{-1}$ (conjugated C:O). Crystallisation from alcohol–light petroleum furnished prisms, m. p. 192°. With ethereal diazoethane this acid regenerated the ethyl ester (IV; R = CO_2Et), m. p. and mixed m. p. 142°.

Ethyl 3-*Ethyl*-4 : 6 : 2′-*trimethyl*-4′-*oxogris*-2′-*ene*-3′-*carboxylate* (XII).—After 1 hr., the foregoing 3-ethylideneoxogrisenecarboxylate (IV; R = CO_2Et) (0·5 g.) in alcohol (200 ml.) containing 5% palladium–charcoal (0·1 g.) no longer absorbed hydrogen. Evaporation of the filtered solution in a vacuum left a glass which crystallised in contact with alcohol and was then recrystallised from light petroleum (charcoal), giving *ethyl* 3-*ethyl*-4 : 6 : 2′-*trimethyl*-4′-*oxogris*-2′-*ene*-3′-*carboxylate* in plates (0·4 g.), m. p. 106°, with infrared absorption at 1675 (unsaturated C:O) and 1745 cm.$^{-1}$ (ester) (Found: C, 73·7; H, 8·0; OEt, 13·3. $C_{19}H_{21}O_3$·OEt requires C, 73·7; H, 7·7; OEt, 13·2%). The 2 : 4-*dinitrophenylhydrazone* separated from alcohol in red prisms, m. p. 216° (Found: C, 62·2; H, 5·9; N, 10·5; OEt, 8·7. $C_{25}H_{25}O_6N_4$·OEt requires C, 62·1; H, 5·8; N, 10·7; OEt, 8·6%).

Methyl 3-*Ethylidene*-4 : 6 : 2′-*trimethyl*-4′-*oxogris*-2′-*ene*-3′-*carboxylate* (IV; R = CO_2Me).—Obtained by the same methods as the corresponding ethyl ester above, this *methyl grisenecarboxylate* formed needles (from methanol), m. p. 162°, having infrared absorption bands at 1675 and 1727 cm.$^{-1}$ (Found: C, 73·8; H, 6·6; OMe, 9·9. $C_{19}H_{19}O_3$·OMe requires C, 73·6; H, 6·8; OMe, 9·5%), and gave the 2 : 4-*dinitrophenylhydrazone* as orange needles, m. p. 244° (from methyl acetate) (Found: C, 61·7; H, 5·1; N, 11·0; OMe, 6·4. $C_{25}H_{23}O_6N_4$·OMe requires C, 61·7; H, 5·2; N, 11·1; OMe, 6·2%), and the *oxime* as prisms, m. p. 220° (from benzene) (Found: C, 70·7; H, 6·9; N, 4·2; OMe, 9·1. $C_{19}H_{20}O_3N$·OMe requires C, 70·4; H, 6·8; N, 4·1; OMe, 9·1%).

3′-*Acetyl*-3-*ethylidene*-4 : 6 : 2′-*trimethylgris*-2′-*en*-4′-*one* (IV; R = Ac).—When the appropriate quantity of the methoxymagnesio-derivative of acetylacetone was used instead of that of acetoacetic ester, β-(3-ethyl-4 : 6-dimethylbenzofur-2-yl)propionic acid (1 g.) was converted by the standard method into 3′-*acetyl*-3-*ethylidene*-4 : 6 : 2′-*trimethylgris*-2′-*en*-4′-*one* which crystallised from aqueous alcohol in plates (0·35 g.), m. p. 167°, $\lambda_{max.}$ 221, 229, 236, 259, 269, 309, 323 mμ (log ε 4·51, 4·55, 4·55, 4·30, 4·21, 3·98, 4·00), having infrared absorption bands at 1681 and 1713 cm.$^{-1}$ (*asym*-enedione) (Found: C, 77·1; H, 7·0. $C_{20}H_{22}O_3$ requires C, 77·4; H, 7·1%).

3-*Ethylidene*-4 : 6 : 2′-*trimethylgris*-2′-*en*-4′-*one* (IV; R = H).—(i) A mixture of 3-ethylidene-4 : 6 : 2′-trimethyl-4′-oxogris-2′-ene-3′-carboxylic acid (0·4 g.), copper bronze (0·08 g.), and quinoline (4 ml.) was kept at 225° for ½ hr., cooled, diluted with ether, and filtered. Quinoline was removed by means of 2N-hydrochloric acid, and acidic impurities by aqueous sodium hydrogen carbonate, whereafter evaporation of the dried (Na_2SO_4) solution gave an oil which,

XUM

when crystallised from light petroleum, gave **3-*ethylidene*-4 : 6 : 2′-*trimethylgris*-2′-*en*-4′-*one*** in rhombs (0·2 g.), m. p. 106°, $\lambda_{max.}$ 228, 235, 256, 263, 266, 306, 314, 317 mμ (log ε 4·57, 4·57, 4·25, 4·14, 4·18, 4·00, 4·00, 4·02), $\nu_{max.}$ 1678 cm.$^{-1}$ (conjugated C:O) (Found: C, 80·6; H, 7·5. $C_{18}H_{20}O_2$ requires C, 80·7; H, 7·4%). The **2 : 4-*dinitrophenylhydrazone*** separated from ethyl acetate in orange needles, m. p. 250—252° (Found: C, 64·4; H, 5·4; N, 12·2. $C_{24}H_{24}O_5N_4$ requires C, 64·3; H, 5·4; N, 12·5%).

(ii) When heated for 10 min. at 200°/20 mm. the grisene-3′-carboxylic acid (IV; R = CO_2H) (0·5 g.) decomposed to carbon dioxide and an oil which supplied the grisenone, m. p. and mixed m. p. 106°, as in (i) above.

(iii) The neutral fraction of the product resulting from maintaining the acetylgrisenone (IV; R = Ac) (0·25 g.) in sulphuric acid monohydrate (3 ml.) at 100° for 3 min. was extracted with boiling light petroleum. The concentrated and cooled extract furnished the grisenone in prisms (0·05 g.), m. p. and mixed m. p. 105°.

(iv) The crude triketone (VIII; R = Et, R′ = Ac) generated as above from β-(3-ethyl-4 : 6-dimethylbenzofur-2-yl)propionic acid (2·5 g.) was treated in methanol (20 ml.) with sodium methoxide (from 0·17 g. of sodium), also in methanol (10 ml.). 15 Hr. later, acidification by acetic acid and evaporation *in vacuo* furnished a viscous oil [crude diketone (VIII; R = Et, R′ = H)] which was cyclised with sulphuric acid monohydrate (5 ml.) at −2° in 1 day. Addition of crushed ice and isolation of the neutral fraction gave the grisenone, m. p. 106°, purified and identified as before.

Ethyl* 4 : 6 : 2′-*Trimethyl*-3-*methylene*-4′-*oxo*-*gris*-2′-*ene*-3′-*carboxylate (IV; R = CO_2Et; CH_2= for Me·CH=).—By the method used for the ethylidene analogue, β-(3 : 4 : 6-trimethylbenzofur-2-yl)propionic acid (3 g.) was converted into the **3-*methylene*-4′-*oxogrisene*-3′-*carboxylate*** which crystallised from alcohol–light petroleum in needles (2·0 g.), m. p. 141°, $\nu_{max.}$ 1681 and 1730 cm.$^{-1}$ (Found: C, 73·6; H, 6·8; OEt, 13·7. $C_{18}H_{17}O_3$·OEt requires C, 73·6; H, 6·8; OEt, 13·8%). The **2 : 4-*dinitrophenylhydrazone*** formed orange needles, m. p. 233°, from ethyl acetate (Found: C, 61·4; H, 5·2; N, 11·1; OEt, 9·0. $C_{24}H_{21}O_6N_4$·OEt requires C, 61·7; H, 5·2; N, 11·1; OEt, 8·9%).

Ozonolysis of Ethyl **3-*Ethylidene*-4 : 6 : 2′-*trimethyl*-4′-*oxogris*-2′-*ene*-3′-*carboxylate* : *Ethyl* 2 : 3 : 4 : 4*a* : 6 : 6*a*-*Hexahydro*-6*a*-*methoxy*-4*a* : 6 : 7 : 9-*tetramethyl*-3-*oxo*-1H-5 : 11-*dioxadibenzo*[a,d]*pentalene*-4-*carboxylate*** (V).—Ozonised oxygen was passed into a solution of ethyl 3-ethylidene-4 : 6 : 2′-trimethyl-4′-oxogris-2′-ene-3′-carboxylate (0·5 g.) in methyl acetate (60 ml.) at −80° for 20 min. Evaporation of the solvent in a vacuum left a gum which did not affect starch–iodide paper and was not decomposed by water. In subsequent experiments this gum was immediately crystallised from methanol and then light petroleum, giving the ***ethyl hexahydro*-3-*oxo*-5 : 11-*dioxadibenzo*[a,d]*pentalene*-4-*carboxylate*** (V) in prisms (0·3 g.), m. p. 136° [Found: On a specimen dried at 120°: C, 67·7; H, 7·2; Alkoxyl as OEt, 23·5. On a specimen fused *in vacuo*: C, 67·5; H, 7·3; Alkoxyl as OEt, 22·5. $C_{19}H_{20}O_4$(OEt)·OMe requires C, 68·0; H, 7·3; Alkoxyl as OEt, 23·5%]. This compound was soluble in 2N-sodium hydroxide, gave red colours with alcoholic ferric chloride and with sulphuric acid, and gave negative reactions in the Zimmermann and Ehrlich tests. The ***oxime*** was prepared in boiling alcohol and crystallised from this solvent in needles, m. p. 221° (decomp.) [Found: C, 65·6; H, 7·1; N, 3·7; Alkoxyl as OMe, 15·1. $C_{19}H_{21}O_4N$(OEt)·OMe requires C, 65·5; H, 7·3; N, 3·5; Alkoxyl as OMe, 15·3%], and resisted conversion into an *iso*oxazolone at all temperatures up to the point of general decomposition.

The mother-liquors from this ozonolysis product contained an oil which was separated by benzene on a silica column into several fractions, none of which yielded pure material, but one of which gave a green colour with nitroprusside in pyridine characteristic of coumaranones.

The ethyl oxogrisene-3′-carboxylate (IV; R = CO_2Et) in carbon tetrachloride gave with ozone a white precipitate which decomposed vigorously near 70°. This solid was decomposed by aqueous alcohol although no pure materials could be isolated and no oxime, 2 : 4-dinitrophenylhydrazone, dimedone derivative, or sodium salt could be prepared.

2 : 3 : 4 : 4*a* : 6 : 6*a*-*Hexahydro*-6*a*-*methoxy*-4*a* : 6 : 7 : 9-*tetramethyl*-3-*oxo*-1H-5 : 11-*dioxadibenzo*[a,d]*pentalene* (XIII).—Ozonolysis of 3-ethylidene-4 : 6 : 2′-trimethyl-4′-oxogris-2′-ene (IV; R = H) (0·3 g.) in methyl acetate (10 ml.) at −80° for 12 min. gave a gum which was unaffected by water but solidified in contact with methanol and then, when purified from light petroleum, supplied the **5 : 11-*dioxadibenzo*[a,d]*pentalene*** (XIII) in plates (0·1 g.), m. p. 128°, $\lambda_{max.}$ 280, 290 mμ (log ε 3·43, 3·47) (Found: C, 72·5; H, 7·8; OMe, 9·1. $C_{18}H_{21}O_3$·OMe requires C, 72·1;

XUM

H, 7·7; OMe, 9·8%). The 2 : 4-*dinitrophenylhydrazone* crystallised in yellow needles, m. p. 211°, from alcohol–ethyl acetate (Found: C, 60·4; H, 5·8; N, 10·9. $C_{25}H_{28}O_7N_4$ requires C, 60·5; H, 5·7; N, 11·3%).

3*a*-2′-*Carboxyethyl*-3-*carboxymethyl*-1 : 3 : 3*a* : 8*b*-*tetrahydro*-8*b*-*methoxy*-1 : 3 : 6 : 8-*tetramethyl*-2 : 4-*dioxa*cyclo*penta*[a]*indene* (XIV).—The above β-oxo-ester (V) (0·85 g.), when kept in 2N-sodium hydroxide (15 ml.) at the b. p. for 1½ hr., gave a cloudy solution from which the neutral oil was extracted into ether. Purification from alcohol–light petroleum then furnished the 5 : 11-dioxadibenzo[*a*,*d*]pentalene (XIII) in plates (0·1 g.), m. p. and mixed m. p. 128°, further identified spectroscopically (Found: C, 71·9; H, 7·6; OMe, 9·8%). The solid precipitated by dilute sulphuric acid from the alkaline solution crystallised from aqueous methanol, affording the *tetrahydro*-2 : 4-*dioxa*cyclo*penta*[a]*indene* (XIV) as rhombs, m. p. 198°, $\lambda_{max.}$ 292 mμ (log ε 3·55), with an infrared absorption band at 1715 cm.$^{-1}$ (CO_2H) [Found: C, 63·2; H, 7·1; OMe, 8·1%; equiv., 183. $C_{17}H_{21}O_3(OMe)(CO_2H)_2$ requires C, 63·5; H, 6·9; OMe, 8·2%; equiv., 189]. After purification by distillation, the *dimethyl ester* (prepared by diazomethane), b. p. 185° (bath)/0·02 mm., formed needles, m. p. 84° [Found: C, 64·8; H, 7·4; OMe, 22·9. $C_{19}H_{24}O_4(OMe)_2$ requires C, 65·0; H, 7·4; OMe, 22·9%].

This diacid was stable to hydrogenolysis (palladium–charcoal) under a wide variety of conditions.

[With J. C. Knight]. *Ethyl* 2 : 3 : 4 : 4*a* : 6 : 6*a*-*Hexahydro*-3-*hydroxy*-6*a*-*methoxy*-4*a* : 6 : 7 : 9-*tetramethyl*-1H-5 : 11-*dioxadibenzo*[a,d]*pentalene*-4-*carboxylate* (XVII).—The β-oxo-ester (V) (0·225 g.) in .ethanol (50 ml.) was reduced by potassium borohydride (0·03 g.) in water (10 ml.). After ½ hr., the solution was acidified (Congo Red) with 2N-sulphuric acid and concentrated. The product was extracted into ether, washed with water, and recovered by evaporation, forming a gum which crystallised from light petroleum, giving the β-*hydroxy-ester* (XVII) in rhombs, m. p. 114°, $\lambda_{max.}$ 283, 290, 293 mμ (log ε 3·47, 3·50, 3·53), $\nu_{max.}$ 3520 (OH) and 1700 cm.$^{-1}$ (ester) [Found: C, 67·7; H, 7·8; Alkoxyl as OMe, 15·9. $C_{19}H_{22}O_4(OEt)$·OMe requires C, 67·7; H, 7·7; Alkoxyl as OMe, 16·6%]. When treated with acetic anhydride and pyridine at 80° for 8 hr. and then at room temperature for 4 days, this alcohol gave the *acetate*, crystallising from methanol in needles, m. p. 162°, after elution from a silica column by benzene–ether (3 : 2) (Found: C, 66·6; H, 7·5. $C_{24}H_{32}O_7$ requires C, 66·7; H, 7·4%). This acetate had a very strong single band at 1742 cm.$^{-1}$ (CO_2Et and OAc) and another at 1250 cm.$^{-1}$ (OAc).

Ethyl 1 : 2 : 3 : 3*a* : 5 : 5*a*-*Hexahydro*-5*a*-*hydroxy*-3*a* : 5 : 6 : 8-*tetramethyl*-2-*oxo*-4 : 10-*dioxa*-cyclo*penta*[d]*benzo*[a]*pentalene* (XV).—From a solution of ethyl 3-ethylidene-4 : 6 : 2′-trimethyl-*cyclo*pent-2′-ene-4′-one-1′-*spiro*-2-benzofuran-3′-carboxylate [1] (II) (0·6 g.) and osmium tetroxide (0·5 g.) in ether (50 ml.) containing pyridine (0·5 ml.) the dark adduct (1·1 g.) separated in 24 hr. The resulting adduct, in 80% methanol (70 ml.) containing charcoal (2 g.), was decomposed by a stream of sulphur dioxide, giving a violet solution which, after filtration, concentration to a small bulk under reduced pressure, and dilution with water, gave a precipitate that was taken up in ether, was washed with water, and recovered as a yellowish oil. This crystallised from aqueous methanol, affording the 4 : 10-*dioxa*cyclo*penta*[d]*benzo*[a]-*pentalenecarboxylate* (XV) in needles or plates, m. p. 147—148°, $\lambda_{max.}$ 208, 226, 278, 288 mμ (log ε 4·62, 4·13, 3·48, 3·49), soluble in dilute sodium hydroxide and having an intense red ferric reaction and infrared absorption bands at 3440 and 1650 cm.$^{-1}$ in the crystalline state and 3440 and 1727 cm.$^{-1}$ when fused (Found: C, 65·5; H, 6·5; OMe, 11·3. $C_{17}H_{17}O_6$·OEt requires C, 65·9; H, 6·4; OMe, 9·0%). The *oxime* formed clusters of needles, m. p. 200° (decomp.), when purified from benzene–methanol and had an infrared absorption band at 1736 cm.$^{-1}$ (ester) (Found: N, 3·6. $C_{19}H_{23}O_6N$ requires N, 3·9%).

The analyses were performed by Mr. A. S. Inglis, M.Sc., and his associates in this Department.

University of Liverpool. [*Received, July 7th*, 1958.]

XUM

919. *Transition-metal Complexes of Seven-membered Ring Systems. Part I. The* cyclo*Heptatriene–Metal Complexes and Related Compounds.*

By E. W. Abel, M. A. Bennett, R. Burton, and G. Wilkinson.

The preparation and properties of *cyclo*heptatriene-chromium and -molybdenum tricarbonyls are described, together with a number of compounds in which a substituent is present on the 1-position of the *cyclo*heptatriene ring. (Di*cyclo*heptatrienyl)di(molybdenum tricarbonyl) and the (di*cyclo*heptatrienyl ether)di(molybdenum tricarbonyl) complex have been prepared. In these two compounds molybdenum tricarbonyl residues are attached to both of the seven-membered rings present. All attempts to attach the tropylium ion to a transition metal in a " sandwich " type of molecule have resulted only in the isolation of di*cyclo*heptatrienyl. A ditropylium hexachloroplatinate, $(C_7H_7)_2PtCl_6$, has been isolated. Infrared spectra of some of these compounds are reported.

A large number of compounds of the type $AM(CO)_n$, where A is a *cyclo*pentadienyl group or an aromatic hydrocarbon and M is a transition metal, have been prepared by the direct reaction of *cyclo*pentadiene [1] or aromatic hydrocarbons [2,3] respectively with numerous metal carbonyls. It has been suggested [4] that the tropylium cation, having the same number of π-electrons as both the *cyclo*pentadienyl anion and the neutral aromatic nucleus, should be able to form a " sandwich " type of bond to a transition metal. In view of the failure to obtain such compounds from reactions with the tropylium ion, discussed below, it was hoped that the reaction of a metal carbonyl with *cyclo*heptatriene would lead to hydrogen loss of a type similar to that which occurs with *cyclo*pentadiene. The reaction of chromium and molybdenum hexacarbonyls with refluxing *cyclo*heptatriene has produced, however, not tropylium compounds, but the *cyclo*heptatriene-chromium and -molybdenum [5] tricarbonyls, $C_7H_8M(CO)_3$ (M = Cr and Mo), in which the hydrocarbon ligand remains intact, without loss of hydrogen:

$$C_7H_8 + M(CO)_6 \longrightarrow C_7H_8M(CO)_3 + 3CO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (I)$$

The *cyclo*heptatriene-metal tricarbonyls form orange-red crystals, which can be sublimed without decomposition, and are soluble in light petroleum, chloroform, benzene, and many other organic solvents. Although in the solid state these compounds may be stored indefinitely, their solutions decompose in air and light, the decomposition being particularly rapid in acetone or alcohol.

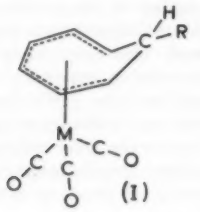
In addition to the two simple *cyclo*heptatriene compounds, a number of compounds (I) have been obtained (Table), in which there is a substituent present on the 1-carbon atom of the *cyclo*heptatriene ring, by methods essentially the same as were used for the simple compounds.

In the light of the formation of substituted arene-metal tricarbonyls,[3] it is interesting that in the reaction between 1-phenyl*cyclo*heptatriene and the metal carbonyls the seven-membered ring takes precedence as donor ligand over the six-membered aromatic ring, the phenyl group acting merely as a ring substituent. That the metal is bound to the seven- and not the six-membered ring, is shown by the fact that the compound is red, as are all the other *cyclo*heptatriene metal carbonyls, and has not the yellow colour of the

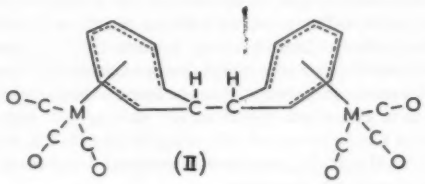
[1] Cf. (*a*) Wilkinson, *J. Amer. Chem. Soc.*, 1954, **76**, 209; (*b*) Fischer and Hafner, *Z. Naturforsch.*, 1954, **9b**, 503; (*c*) Piper, Cotton, and Wilkinson, *J. Inorg. Nuclear Chem.*, 1955, **1**, 165.
[2] Natta, Ercoli, and Calderazza, *Chimica e Industria*, 1958, **40**, 287; *Angew. Chem.*, 1958, **70**, 322.
[3] Nicholls and Whitting, *Proc. Chem. Soc.*, 1958, 152.
[4] Piper and Wilkinson, *J. Inorg. Nuclear Chem.*, 1956, **3**, 104.
[5] Abel, Bennett, and Wilkinson, *Proc. Chem. Soc.*, 1958, 152.

arene-metal carbonyls.[3] Further, whereas the latter have only two carbonyl stretching modes, the *cyclo*heptatriene derivatives have three.

A limited time of reaction between di*cyclo*heptatrienyl and molybdenum carbonyl formed the monomolybdenum tricarbonyl complex, in which a molybdenum tricarbonyl residue is attached to one ring only. A longer reaction time has produced the bis(molybdenum tricarbonyl) complex (II), in which both rings are attached to molybdenum tricarbonyl residues In a similar manner it has been possible to isolate the compound



(I)



(II)

(di*cyclo*heptatrienyl ether)di(molybdenum tricarbonyl). These binuclear compounds are much less soluble in organic solvents than are the mononuclear ones. The compounds prepared and some of their properties are given in the Table).

Attempts to obtain compounds with the tropylium cation bound to a transition metal have been unsuccessful. Interaction of tropylium bromide and sodium manganese carbonyl in tetrahydrofuran resulted in the quantitative formation of di*cyclo*heptatrienyl and manganese carbonyl:

$$2NaMn(CO)_5 + 2C_7H_7Br \longrightarrow C_{14}H_{14} + 2NaBr + Mn_2(CO)_{10} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Similarly, di*cyclo*heptatrienyl is formed in the reaction between potassium iron carbonyl hydride or mercury iron carbonyl with tropylium bromide. Addition of tropylium bromide to ethanolic solutions of hexachloroplatinic acid gave an immediate brown precipitate of empirical formula $(C_7H_7)_2PtCl_6$, insoluble in water, ethanol, chloroform, and benzene; this product was undoubtedly ditropylium hexachloroplatinate.

Infrared spectra in the carbonyl region of the hydrocarbon metal compounds.

Compound	M. p.	C–O stretches, cm.$^{-1}$
$Cr(CO)_3$–*cyclo*heptatriene	128—130° (dec.)	1991, 1921, 1893
$Mo(CO)_3$–*cyclo*heptatriene	100	2000, 1929, 1895
$Cr(CO)_3$–di*cyclo*heptatrienyl †	—	1990, 1927, 1895
$Mo(CO)_3$–di*cyclo*heptatrienyl	*	1998, 1929, 1898
$Cr(CO)_3$–methyl*cyclo*heptatriene	72—73	1990, 1921, 1893
$Mo(CO)_3$–methyl*cyclo*heptatriene	*	2001, 1929, 1896
$Cr(CO)_3$–phenyl*cyclo*heptatriene †	—	1989, 1921, 1890
$Mo(CO)_3$–phenyl*cyclo*heptatriene	*	2000, 1926, 1897
$[Mo(CO)_3]_2$–di*cyclo*heptatrienyl	*	1991, 1928, 1889
$[Mo(CO)_3]_2$–di*cyclo*heptatrienyl ether	*	1993, 1928, 1889

* Decompose above 150° without melting. † Insufficient for analysis.

Attempts to carry out substitution in the aromatic ring by methods successfully applied to ferrocene [6] (*e.g.*, Friedel–Crafts reactions, sulphonation, etc.) failed, owing to fission of the metal–ring bond and complete decomposition of the molecule. Attempts to replace the three remaining carbonyl groups by other ligands also failed. However, with a number of ligands (trialkyl- or triaryl-phosphines; amines; arsines), the reaction has produced a series of compounds $L_3Mo(CO)_3$, *e.g.*, $(Ph_3As)_3Mo(CO)_3$, in which it may reasonably be assumed that the carbon monoxide groups are *cis* to each other: these will be discussed in a later paper.

[6] Rausch, Vogel, and Rosenburg, *J. Chem. Educ.*, 1957, **34**, 268.

Structure of the Compounds.—Nuclear magnetic resonance studies,[7,8] and measurements of vibrational spectra,[9] of *cyclo*heptatriene suggest that the six olefinic carbon atoms in the molecule are almost planar, and that the six π-electrons present form a delocalized system which to some extent " by-passes " the methylene group to give a quasi-aromatic system. The bonding of the *cyclo*heptatriene nucleus to the metal atoms must be due to the overlap of the *d*-orbitals of the metal with the delocalized π-electron density of the ring. A similar type of bonding has also been proposed for butadieneiron tricarbonyl.[10] In both the latter and the present type of complex the metal atom can formally be considered as having attained an inert-gas structure. Although, as in the well-known *cyclo*pentadienyl- and arene-metal complexes,[11] the electronic structure is more complicated than this simple view suggests, it is not to be assumed that all of the six π-electrons have abandoned the ring for the metal atom.

The *cyclo*pentadienyl- and arene-metal compounds of similar formula, *e.g.*, $C_5H_5Mn(CO)_3$ and $C_6H_6Cr(CO)_3$, irrespective of the presence of substituents on the ring and the total symmetry of the molecules, show only two strong C–O stretching modes, in keeping with the local symmetry of the carbon monoxide groups. There is now evidence for free rotation of the *cyclo*pentadienyl and arene rings about the metal–ring axis from various physical measurements on di(π-*cyclo*pentadienyl) and diarene compounds (see ref. 11), and the infrared data of the carbonyls are also consistent with this view. In the *cyclo*heptatriene derivatives, however, three strong C–O stretching modes are always observed (see Table). In view of the incomplete delocalization of the π-electron system, free rotation about the metal–ring axis is perhaps not to be expected, and the *cyclo*heptatriene-metal carbonyls thus have the ring fixed with respect to the carbon monoxide groups, giving a lower symmetry to the molecules than in the *cyclo*pentadienyl and arene analogues. One carbon monoxide group could lie along the plane of symmetry of the ring, and the other two at an angle to it; whatever the exact disposition, three infrared-active carbonyl modes would result. The *cyclo*heptatriene-metal compounds are thus formulated as (I), where the disposition of the carbonyl groups relative to the ring is merely symbolic.

Experimental

Microanalyses are by the Microanalytical Laboratory of Imperial College. Infrared spectra were recorded on a Model 21 Perkin–Elmer double-beam spectrometer with sodium chloride optics. Phenyl*cyclo*heptatriene,[12] tropylium bromide,[13] di*cyclo*heptatrienyl ether,[12] and di*cyclo*heptatrienyl [13] were prepared by methods described previously. Whilst the existence of methyl*cyclo*heptatriene has been noted,[14] preparative details and characterization have not previously been recorded.

1-*Methyl*cyclo*heptatriene*.—Finely powdered tropylium bromide (4·0 g.) was gradually added to a solution of methylmagnesium iodide (from 0·8 g. of magnesium and 4·7 g. of methyl iodide) in ether (75 c.c.). After rapid stirring for 1 hr. at 20° the mixture was refluxed for 0·5 hr., then excess of the Grignard reagent was decomposed by water (40 c.c.). Removal of solvent from the ether layer at 20°/50 mm. and subsequent distillation gave 1-*methyl*cyclo*heptatriene* (1·04 g.), b. p. 50°/35 mm., n_D^{20} 1·5050 (Found: C, 89·7; H, 9·7. C_8H_{10} requires C, 90·6; H, 9·4%).

Preparation of the Hydrocarbon–Metal Complexes.—The preparation of the compounds was similar in all cases. The metal carbonyl was heated under reflux in nitrogen with the pure hydrocarbon, or with a solution of the hydrocarbon in light petroleum (b. p. 100—120°). Reaction times for reaction of *cyclo*heptatriene varied from 7 hr. with molybdenum carbonyl

[7] Corey, Burke, and Remers, *J. Amer. Chem. Soc.*, 1955, **77**, 4941.
[8] Doering, Laber, Vonderwahl, Chamberlain, and Williams, *ibid.*, 1956, **78**, 5448.
[9] R. C. Lord, personal communication; M. V. Evans, Ph.D. Thesis, Massachusetts Institute of Technology.
[10] Hallam and Pauson, *J.*, 1958, 642.
[11] Cf. Liehr and Ballhausen, *Acta Chem. Scand.*, 1957, **11**, 207.
[12] Doering and Knox, *J. Amer. Chem. Soc.*, 1954, **76**, 3203.
[13] *Idem, ibid.*, 1957, **79**, 352.
[14] Doering and Krauch, *Angew. Chem.*, 1956, **68**, 661.

XUM

to 15 hr. with chromium carbonyl. After this time the hydrocarbon and solvent were removed in a vacuum, and excess of the carbonyl sublimed from the residue at 40°/0·05 mm. The residues were extracted with light petroleum, and the solutions filtered and cooled to −60°. The *products* recrystallized from light petroleum (see Table).

R in R–M(CO)$_3$	M in R·M(CO)$_3$	Found (%) C	H	M	O	Required (%) C	H	M	O
*cyclo*Heptatriene	Mo	44·2	3·1	34·9	17·6	44·1	3·0	35·3	17·6
,, ...	Cr	52·8	3·6	—	21·2	52·6	3·5	—	21·0
Methyl*cyclo*heptatriene ...	Mo	46·0	4·1	—	16·8	46·2	3·5	—	16·8
,, ...	Cr	53·3	4·7	—	—	54·6	4·1	—	—
Phenyl*cyclo*heptatriene ...	Mo	55·1	3·9	—	15·3	55·2	3·5	—	13·8
,, ...	Cr *	—	—	—	—	—	—	—	—
Di*cyclo*heptatrienyl	Mo	56·5	4·2	—	13·6	56·4	3·9	—	13·3
,, ...	Cr *	—	—	—	—	—	—	—	—

* Insufficient crystals were obtained for analysis, but carbonyl modes in infrared spectra were recorded.

The infrared spectrum of $C_7H_8Mo(CO)_3$, in addition to the very strong carbonyl peaks, shows absorption at 3020m, 2938m, 2861s, 2821s, 1462vs, 1440vs, 1402s, 1358s, 1313vs, 940s, and 920m cm.$^{-1}$.

*Prolonged Interaction of Dicyclo**heptatrienyl** and Molybdenum Hexacarbonyl.*—The hydrocarbon (0·19 g.) and carbonyl (0·56 g.) were refluxed for 36 hr. in light petroleum (b. p. 100—120°; 50 c.c.). The solvent was removed at 20°/0·5 mm. and excess of molybdenum carbonyl and di*cyclo*heptatrienyl were sublimed at 60°/0·1 mm. from the residue. The remaining solid was washed with light petroleum to remove the (di*cyclo*heptatrienyl)molybdenum tricarbonyl formed in the reaction; the light brown residue (0·3 g.) was extracted with hot chloroform (3 × 25 c.c.). Concentration of the combined extracts and cooling to −20° gave (*dicyclo**heptatrienyl*)*di*(*molybdenum tricarbonyl*) (0·03 g.) (Found: C, 43·5; H, 3·1; O, 17·7; Mo, 35·5%; *M*, 517. $C_{20}H_{14}O_6Mo_2$ requires C, 44·3; H, 2·6; O, 17·7; Mo, 35·5%; *M*, 542) as small red crystals.

*Interaction of Molybdenum Hexacarbonyl and Dicyclo**heptatrienyl Ether**.*—The ether (0·79 g.) and the carbonyl (2·1 g.) were refluxed for 15 hr. in light petroleum (b. p. 100—120°; 50 c.c.). After removal of solvent at 20°/0·5 mm. and sublimation of unchanged molybdenum hexacarbonyl at 75°/0·1 mm., the residue was washed with light petroleum (4 × 20 c.c.) and then extracted with hot chloroform (3 × 25 c.c.). Evaporation of the combined chloroform extracts to about 20 c.c., followed by cooling to −20°, gave (*dicyclo**heptatrienyl ether*)*di*(*molybdenum tricarbonyl*) (0·06 g.) (Found: C, 44·3; H, 2·4; O, 20·4; Mo, 34·2%; *M*, 535. $C_{20}H_{14}O_7Mo_2$ requires C, 42·9; H, 2·5; O, 20·1; Mo, 34·4%; *M*, 558).

Interaction of Potassium Iron Carbonyl Hydride and Tropylium Bromide.—Potassium iron carbonyl hydride was produced by the rapid stirring of iron pentacarbonyl (6·0 g.) with potassium hydroxide (5·2 g.) in water (50 c.c.) under an atmosphere of nitrogen. To this solution was added tropylium bromide (5·2 g.), and stirring was continued for 4 hr. After complete removal of solvent at 40°/0·1 mm., the crude solid product was sublimed at 70°/0·1 mm. Chromatography of the light green sublimate in light petroleum yielded di*cyclo*heptatrienyl (0·1 g.), m. p. 61°. The green colour of the sublimate was shown (infrared spectrum) to be due to a small amount of iron dodecacarbonyl which was destroyed during the chromatography.

Interaction of Sodium Manganese Carbonyl and Tropylium Bromide.—The carbonyl (2·24 g., 1 mol.) in tetrahydrofuran (75 c.c.) was added to finely powdered 15% sodium amalgam (5 g.) and the whole was stirred for 4 hr. After filtration in a dry nitrogen atmosphere, the resulting dark green solution was added to tropylium bromide (2·0 g., 2 mol.) in tetrahydrofuran (50 c.c.) and the mixture stirred for 2 hr. After removal of solvent at 25°/0·2 mm., the solid residue was sublimed at 70°/0·1 mm., to give white and yellow crystals. Chromatography in light petroleum on alumina gave manganese carbonyl (1·93 g., 86%) and di*cyclo*heptatrienyl (0·89 g., 82%), m. p. 60° (Found: C, 92·0; H, 8·2%; *M*, 176. Calc for $C_{14}H_{14}$: C, 92·3; H, 7·7%; *M*, 182). The organic product was found to be identical with that obtained by Doering and Knox's method.[13]

Interaction of Mercury Iron Carbonyl and Tropylium Bromide.—The carbonyl (2·15 g.) and the bromide (0·8 g.) were refluxed for 3 hr. in tetrahydrofuran (75 c.c.) under nitrogen. The

solvent was removed at 25°/0·5 mm., and the residue extracted with light petroleum (4 × 30 c.c.). Concentration of the combined extracts gave di*cyclo*heptatrienyl (0·25 g., 59%), m. p. 59—61°.

Preparation of Ditropylium Hexachloroplatinate.—A solution of tropylium bromide (2 g.) in aqueous ethanol (50 c.c.) was added at 20° to an aqueous-ethanolic solution (50 c.c.) of hexachloroplatinic acid (from 4 g. of platinum tetrachloride). The precipitate, which was formed immediately, was filtered off and washed with alcohol and then ether. Removal of solvent at 20°/0·2 mm. left pure *ditropylium hexachloroplatinate* (2·5 g., 75%) (Found: C, 28·7; H, 2·4; Cl, 36·0; Pt, 32·9. $C_{14}H_{14}Cl_6Pt$ requires C, 28·5; H, 2·4; Cl, 36·1; Pt, 33·1%), as a light brown microcrystalline powder.

Catalytic Hydrogenations.—These were carried out with hydrogen and Adams platinum catalyst in ethyl acetate. *cyclo*Heptatriene absorbed 3 mols. of hydrogen in 15 min. The *cyclo*heptatriene-chromium and -molybdenum tricarbonyls, however, were recovered (88 and 90% respectively) after similar treatment for 3 hr.

We thank the Department of Scientific and Industrial Research (R. B.) and the Ethyl Corporation (E. W. A. and M. A. B.) for financial support. Gifts of molybdenum hexacarbonyl (Climax Molybdenum Company), chromium hexacarbonyl (Ethyl Corporation), and *cyclo*heptatriene (Shell Petroleum Company Ltd.) are gratefully acknowledged.

Inorganic Chemistry Laboratories, Imperial College of Science and Technology, London, S.W.7. [*Received, July 28th*, 1958.]

---

920. *The Activation of Carbon–Carbon Double Bonds by Cationic Catalysts. Part VI.* Effect of Substituents on the Dimerisation of 1 : 1-Diarylethylenes catalysed by Trichloroacetic Acid.*

By Alwyn G. Evans, Peter M. S. Jones, and J. H. Thomas.

The kinetics and equilibria for the dimerisation of 1-*p*-bromophenyl-1-phenylethylene catalysed by trichloroacetic acid in benzene have been studied dilatometrically, thus extending our previous work.[1a, 1b] The olefins 1 : 1-di-*o*-tolylethylene and 1 : 1-di-*o*-methoxyphenylethylene do not dimerise in trichloroacetic acid–benzene solutions, and we suggest this to be due to steric blocking by the bulky *ortho*-groups. The effect of *para*-substituents on the thermodynamic constants for the dimerisation of 1 : 1-diarylethylenes by trichloroacetic acid in benzene is discussed.

Experimental

Materials.—Trichloroacetic acid and benzene were purified as before.[1a]

1-p-*Bromophenyl*-1-*phenylethylene.* 1-*p*-Bromophenyl-1-phenylethanol was prepared by the action of *p*-bromoacetophenone on phenylmagnesium bromide in dry ether. It was extracted and steam-distilled to remove volatile impurities, and the residual alcohol distilled twice under reduced pressure to dehydrate it. The middle fraction of olefin (b. p. 145—150°/1—2 mm.; lit.[2] b. p. 200°/19 mm.) [Found: *M* (cryoscopic in benzene), 247·2. Calc. for $C_{14}H_{11}Br$: *M*, 259. Purity at least 95%] was redistilled under high vacuum in a one-piece glass apparatus,[1a, 1b] the colourless oil being kept under vacuum until required.

1 : 3-Di-*p*-bromophenyl-1 : 3-diphenylbut-1-ene was prepared from 1-*p*-bromophenyl-1-phenylethylene by the action of either concentrated sulphuric acid in acetic acid or trichloroacetic acid in benzene, as for the dimer of 1 : 1-diphenylethylene.[1a] The product was a viscous oil which, unlike the monomer, was insoluble in acetic acid, with which it was washed. It was distilled under high vacuum in a one-piece glass apparatus, the product setting to a glass [Found, *M* 510 (for both methods of preparation). Calc. for $C_{28}H_{22}Br_2$: *M*, 518]. By analogy with the olefins studied previously [1a, 1b] we assume this to be the but-1-ene dimer, and not the

* Part V, A. G. Evans and J. Lewis, *J.*, 1957, 2975.

[1] (*a*) Part I, A. G. Evans, N. Jones, and J. H. Thomas, *J.*, 1955, 1824; (*b*) A. G. Evans, P. M. S. Jones, and J. H. Thomas, *J.*, 1956, 2757.

[2] Stenner and Simon, *Ber.*, 1904, **37**, 4168.

indane (see below). This dimer can possess both optical and geometrical isomerism, and may be a mixture of 4 isomers, which could account for its remaining as an oil.

1 : 1-*Di-o-tolylethylene.* 1 : 1-Di-*o*-tolylethanol, from ethyl acetate and *o*-tolylmagnesium bromide, was dehydrated and the 1 : 1-di-*o*-tolylethylene purified as for 1 : 1-di-*p*-tolylethylene [1b] (m. p. 40—41°; lit.,[3] m. p. 42·6°).

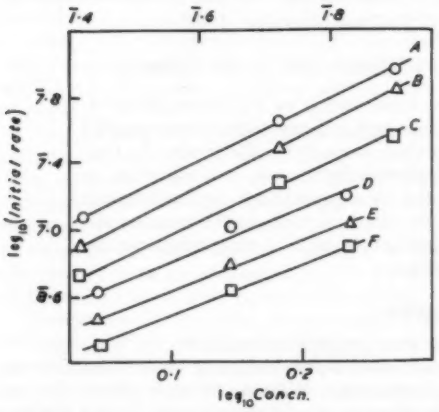
1 : 1-*Di-o-methoxyphenylethylene.* 1 : 1-Di-*o*-methoxyphenylethanol, from ethyl acetate and *o*-methoxyphenylmagnesium bromide, was recrystallised several times from light petroleum (b. p. 60—80°). The pure alcohol, m. p. 124—125° (lit.,[4] m. p. 125°), did not lose water on vacuum distillation, so we used Bergman and Bondi's method [4] (sulphuric–acetic acid). The crude olefin was recrystallised seven times from absolute ethanol–benzene, the final product having m. p. 90—91° (lit.,[4] m. p. 90°) [Found: *M* (cryoscopic in benzene), 238. Calc. for $C_{16}H_{16}O_2$: *M*, 240].

Technique.—The procedure for preparing the olefin–acid–benzene solutions, and following their volume change dilatometrically, was identical with that used in Part I.[1a]

Results

1. *The* 1-p-*Bromophenyl*-1-*phenylethylene–Trichloroacetic acid–Benzene System.*—(*a*) *Products.* Solutions of the olefin in benzene do not change in volume, but in the presence of trichloroacetic acid the solutions become pale green and their volumes decrease with time to a

FIG. 1. *Orders in reagents for initial rate of dimerisation of* 1-p-*bromophenyl*-1-*phenylethylene*
The initial rate is expressed in terms of moles of dimer formed or lost per l. per sec. Concns. in moles $l.^{-1}$ *at* 19°.



	Curve	Temp.	[AH]
A	Top scale,	54·5°	1·34
B	$\log_{10}$ [Initial	45·9	1·35
C	monomer]	33·8	1·37
			Initial monomer
D	Bottom scale,	54·5	0·248
E	$\log_{10}$ [AH]	45·9	0·251
F		33·8	0·255

steady value. Density measurements on separate solutions of the monomer and the high vacuum-distilled dimer oil in benzene (see Part I [1a]) gave the following volume changes for the complete conversion of 1 mole of monomer into 0·5 mole of dimer in 1 l. of solution: 11·87 ml. at 33·8°, 11·85 ml. at 45·9°, and 12·60 ml. at 54·6°. These values agree closely with those for the dimerisation of 1 : 1-diphenylethylene,[1a] 1 : 1-di-*p*-tolylethylene,[1b] and 1-*p*-methoxyphenyl-1-phenylethylene,[1b] all in benzene, and this helps to confirm the identity of the dimer oil as 1 : 3-di-*p*-bromophenyl-1 : 3-diphenylethylene.

The quantity of trichloroacetic acid titratable with sodium hydroxide after reaction is equal within experimental error (±2%) to the original.

The benzene solutions, after removal of the acid and evaporation in a high vacuum, deposited a viscous oil which was washed several times with acetic acid to remove traces of monomer, and dried under vacuum. Its weight agreed to within 5% with that of the dimer expected to be present from the volume change.

[3] Coops, Hoijtink, Kramer, and Faber, *Rec. Trav. chim.*, 1953, **72**, 765.
[4] Bergman and Bondi, *Ber.*, 1931, **64**, 1455.

(*b*) *Rate constants.* The initial rates of dimerisation were measured from volume–time plots as described in Part I. The acid orders were found from the slopes of plots of $\log_{10}$ (Initial rate) against $\log_{10}$ [Acid] at constant initial olefin concentrations {see Fig. 1, curves *D*, *E*, and *F* (where [AH] is the concentration of trichloroacetic acid *dimer*}: and the monomer orders similarly from plots of $\log_{10}$ (Initial rate) against $\log_{10}$ [Initial monomer] at constant [AH] (see Fig. 1, curves *A*, *B*, and *C*). The acid and olefin orders thus found are given in Table 1; the

TABLE 1. *Reagent orders, initial rate constants, and energy and entropy of activation for the dimerisation of* 1-p-*bromophenyl*-1-*phenylethylene.*

Temp.	Acid order	Olefin order	$10^7 k_f$ (mole^{-4} l.^{4} sec.$^{-1}$)	E_f (kcal. mole^{-1})	A_f (mole^{-4} l.^{4} sec.$^{-1}$)	K (mole^{-1} l.)
33·8°	3·1	1·95	2·6		24·9	33·8 ± 2
45·9	3·2	2·0	5·4	11·2 ± 0·5	25·8	17·1 ± 2
54·5	3·1	2·0	7·4		22·1	8·1 ± 2

mean values are 3·1 ± 0·2 and 2·0 ± 0·2 respectively. Thus the initial rate of dimerisation is k_f[M]^2[AH]^3, where k_f is the (forward) rate constant and [M] the initial monomer concentration. The mean values of k_f thus found are given in Table 1.

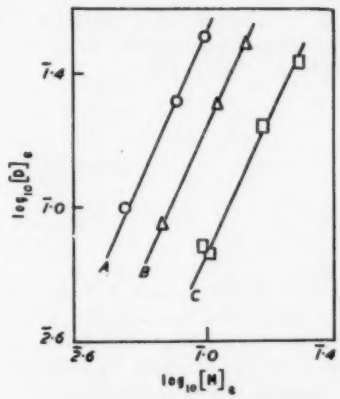


FIG. 2. *Relationship between* $[D]_e$ *and* $[M]_e$ *for* 1-p-*bromophenyl*-1-*phenylethylene.*
Curves *A*, *B*, and *C* are for solutions at 33·8°, 45·9°, and 54·6° respectively.

The mean activation energy for the dimerisation, E_f, found from the dependence of log k_f on $1/T$, is given in Table 1, together with values of the temperature-independent factor, A_f. In Table 2 these results are expressed as the free energy of activation, $\Delta G_f^{\ddagger}$, the enthalpy of activation $\Delta H_f^{\ddagger}$ ($= E_f - \boldsymbol{RT}$), and the entropy of activation $\Delta S_f^{\ddagger}$.

TABLE 2. *Thermodynamic constants for the dimerisation of* R·C$_6$H$_4$·C(C$_6$H$_4$R′):CH$_2$.

Rate-determining step	R	R′	$+\Delta G^\circ$ (kcal. mole^{-1})	$+\Delta H^\circ$ (kcal. mole^{-1})	$+\Delta S^\circ$ (cal. deg.$^{-1}$ mole^{-1})	$+\Delta G_f^{\ddagger}$ ($\Delta G_{1a}^\circ + \Delta G_{2a}^{\ddagger}$) (kcal. mole^{-1})	$+\Delta H_f^{\ddagger}$ ($\Delta H_{1a}^\circ + \Delta H_{2a}^{\ddagger}$) (kcal. mole^{-1})	$+\Delta S_f^{\ddagger}$ ($\Delta S_{1a}^\circ + \Delta S_{2a}^{\ddagger}$) (cal. deg.$^{-1}$ mole^{-1})
Reaction 2*a*	*p*-Br	H	−2·16	−14·0	−38·6	27·2	10·6	−54
	H	H	−1·69	−10·1	−27·4	26·0	8·5	−57
	p-Me	*p*-Me	−1·41	−8·4	−22·8	22·6	6·0	−54
	p-MeO	H	−1·32	−6·0	−15·3	22·1	4·6	−57
						$\Delta G_f^{\ddagger}$ ($\Delta G_{1a}^{\ddagger}$)	$\Delta H_f^{\ddagger}$ ($\Delta H_{1a}^{\ddagger}$)	$\Delta S_f^{\ddagger}$ ($\Delta S_{1a}^{\ddagger}$)
Reaction 1*a*	*p*-MeO	*p*-MeO	−0·93	−3·3	−7·8	18·4	8·8	−31·3

Values of ΔG°, $\Delta G_f^{\ddagger}$, ΔS°, and $\Delta S_f^{\ddagger}$ are quoted for the standard state 1 mole l.$^{-1}$ at 33·8° c.

(*c*) *Equilibrium constants.* The equilibrium concentrations of monomer, $[M]_e$, and dimer, $[D]_e$, were found (as in Part I [1a]) from the equilibrium volume changes. The latter were independent of the acid concentration, showing that the orders in acid for the forward and the reverse reaction were the same. Plots of $\log_{10}$ $[D]_e$ against $\log_{10}$ $[M]_e$ (Fig. 2) are all of slope 2 ± 0·02, showing that the ratio of monomer order to dimer order is 2 over this temperature

range. The mean equilibrium constants $K = [D]_e/[M]_e^2$ are given in Table 1. The exothermicity of the dimerisation ($-\Delta H°$) was found from the slope of a plot of $\log_{10}$ (mean K) against $1/T$ to be $14{\cdot}0 \pm 0{\cdot}7$ kcal. mole^{-1}. Table 2 also gives the free-energy change, $\Delta G°$ ($= -RT \ln K$), and the entropy change, $\Delta S°$, accompanying the dimerisation at 33·8°.

2. *Attempted Dimerisation of* 1 : 1-*Di-o-tolylethylene.*—The volume of a solution (33·2 ml.) of 1 : 1-di-*o*-tolylethylene (0·115 mole l.$^{-1}$) and trichloroacetic acid (0·346 mole l.$^{-1}$) in benzene did not change at 45·9° during several months, after which all ($\pm 2\%$) of the acid was recovered. All the olefin was recovered as described previously and, after one crystallisation, had the m. p. of the monomer. The solution became intensely blue during the time of observation ($\lambda_{max.} = 598$ mμ).

3. *Attempted Dimerisation of* 1 : 1-*Di-o-methoxyphenylethylene.*—The volume (32·7 ml.) of a solution of 1 : 1-di-*o*-methoxyphenylethylene (0·229 mole l.$^{-1}$) and trichloroacetic acid (0·101 mole l.$^{-1}$) in benzene did not change during 3 months at 45·9°, after which monomer and acid were completely recovered.

Discussion

1. *Dimerisation of* 1-p-*Bromophenyl*-1-*phenylethylene.*—The order in acid, 3, and in olefin, 2, for the rate of dimerisation, and the dependence of the position of equilibrium on total olefin concentration, show that this olefin reacts by the same mechanism as does 1 : 1-diphenylethylene:[1a,1b]

$$3AH + M + M \underset{b}{\overset{a}{\rightleftharpoons}} (HM^+A^-)_{solv.2AH} + M \quad \ldots\ldots\ldots (1)$$

$$(HM^+A^-)_{solv.2AH} + M \underset{b}{\overset{a}{\rightleftharpoons}} (HD^+A^-)_{solv.2AH} \quad \ldots\ldots\ldots (2)$$

$$(HD^+A^-)_{solv.2AH} \underset{b}{\overset{a}{\rightleftharpoons}} D + 3AH \quad \ldots\ldots\ldots (3)$$

The rate-controlling step of the dimerisation is reaction 2*a*, *i.e.*, $k_f = K_1 k_{2a}$, $\Delta G_f^{\ddagger} = \Delta G_{1a}° + \Delta G_{2a}^{\ddagger}$, $\Delta H_f^{\ddagger} = \Delta H_{1a}° + \Delta H_{2a}^{\ddagger}$, and $\Delta S_f^{\ddagger} = \Delta S_{1a}° + \Delta S_{2a}^{\ddagger}$. In Table 2 we give our results for the dimerisation of 1-*p*-bromophenyl-1-phenylethylene together with our previous results for various *para*-substituted 1 : 1-diphenylethylenes.[1a,1b] These results may be discussed as follows.

2. *Effect of* para-*Substituents on the Dimerisation Equilibrium.*—(a) *Energy considerations.* Table 2 shows that an increase in the electron-releasing power of the *para*-substituents down the series 1-*p*-Br, unsubstituted, 1 : 1-di-*p*-CH_3, 1-*p*-MeO, 1 : 1-di-*p*-MeO decreases the exothermicity ($-\Delta H°$) of the dimerisation. That is, an electron-releasing *para*-group stabilises the final state of reaction 3, D + 3AH, less than it stabilises the initial state of reaction 1, M + M + 3AH. Since the change from M + M + 3AH to D + 3AH, involves the loss of a double bond, it appears that the olefin double bond (which is conjugated with two benzene rings) is stabilised by the presence of an electron-releasing *para*-substituent. The more the olefin double bond is stabilised, the more energetically favourable is M + M + 3AH which involves two olefins than D + 3AH which involves only one (see Fig. 3).

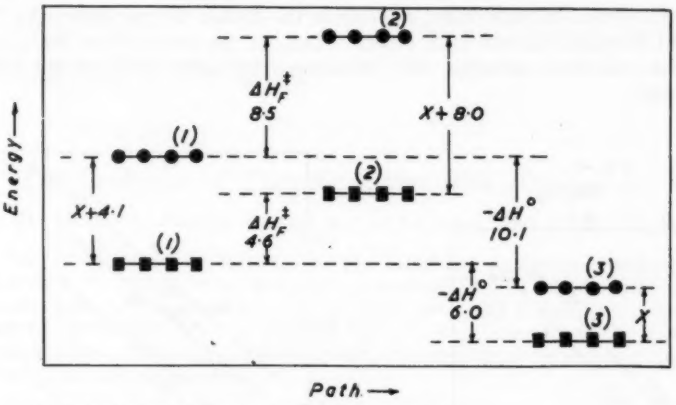
(b) *Entropy considerations.* An increase in the electron-releasing power of the *para*-substituent causes $\Delta S°$, the entropy change from M + M + 3AH to D + 3AH, to become more positive, partly offsetting the decrease in exothermicity, and thus making the decrease in K, and the positive increase in $\Delta G°$, small.

3. *Effect of* para-*Substituents on those Dimerisation Reactions for which Reaction* 2*a is Rate-determining.*—(a) *Energy considerations.* Table 2 shows that here an increase in the electron-releasing power of the *para*-substituents decreases the activation enthalpy for the forward reaction, $\Delta H_f^{\ddagger} (= E_f - RT)$. That is, an electron-releasing *para*-substituent stabilises the transition state of reaction 2*a* more than it stabilises M + M + 3AH (see Fig. 3). This may be because, for the reaction between two olefins containing conjugated

double bonds there is resonance energy in the transition state; [5] the π-electrons are more mobile in the transition state because there are more carbon centres available for them. A similar increase in electron mobility is possible in the transition state of reaction 2*a* where a monomer molecule and a monomer ion are pushed close together (I) and the 26 electrons can move in the field of 27 nuclei (II).

(b) *Entropy considerations.* A change in the electron-releasing power of the *para*-substituent has no effect on the entropy of activation, $\Delta S_f^{\ddagger}$, that is, on the entropy change from M + M + 3AH to the transition state of reaction 2*a*. This is different from the

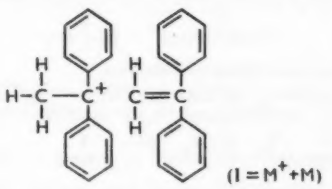
FIG. 3. *Diagram of the reaction paths for dimerisation of* (●) 1 : 1-*diphenylethylene and* ■ 1-p-*methoxyphenyl*-1-*phenylethylene.*



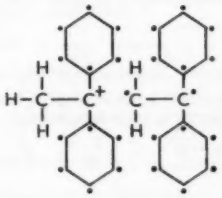
(1) Initial state of reaction 1*a*, M + M + 3AH.
(2) Transition state of reaction 2.
(3) Final state of reaction 3, D + 3AH.

X is an arbitrary value for the stabilisation of the dimer double bond due to the introduction of a *p*-MeO substituent.

effect of these groups on the total entropy change ΔS° from M + M + 3AH to D + 3AH (section 2b). Our results show, therefore, that the effect of electron-releasing groups on



(I = M^++M)



(II)

the entropy of the transition state of reaction 2*a* is different from their effect on the entropy of D + 3AH. We cannot yet interpret this difference.

4. *Dimerisation when Reaction* 1*a is Rate-determining.*—As more powerful electron-releasing *para*-groups are introduced into the olefin, at one point the mechanism of dimerisation changes. The order in monomer changes from 2 to 1, that is, the rate-determining step changes from reaction 2*a* to reaction 1*a*. This occurs between 1-*p*-methoxyphenyl-1-phenylethylene and 1 : 1-di-*p*-methoxyphenylethylene [1b] (Table 2). This means that the stabilisation by electron-releasing *para*-groups is greater for the

[5] M. G. Evans and Warhurst, *Trans. Faraday Soc.*, 1938, **34**, 614; M. G. Evans, *Trans. Faraday Soc.*, 1939, **35**, 832.

transition state of reaction 2*a*, in which a monomer molecule and a monomer ion are pushed close together, than for that of reaction 1*a* in which the two olefins are, as yet, independent. Introduction of more powerful electron-releasing *para*-groups not only reduces the energy of the transition state of reaction 2*a* faster than that of the initial state of reaction 1*a*, but also faster than that of the transition state of reaction 1*a*. Thus, eventually, the transition state of reaction 1*a* lies higher in energy than that of reaction 2*a*, and the rate-determining step becomes reaction 1*a* instead of reaction 2*a*. This change does not occur just when the energy of the transition state of reaction 2*a* falls below that of reaction 1*a*, but when the free energy of the former falls below that of the latter. The entropy of the transition state of reaction 1*a* is more positive than that of the transition state of reaction 2*a*, since in the latter case two molecules of monomer are specially oriented with respect to each other, whereas in the former the two molecules of monomer have not yet been pushed into each other. Thus, at the point where the change occurs (Table 2) the activation enthalpy, $\Delta H_t^{\ddagger}$, increases appreciably, although the free energy of activation falls.

FIG. 4.

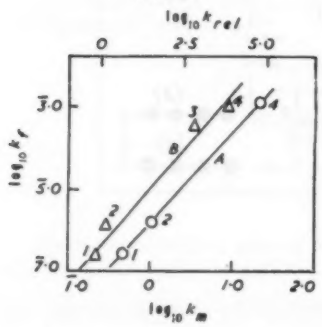


FIG. 5.

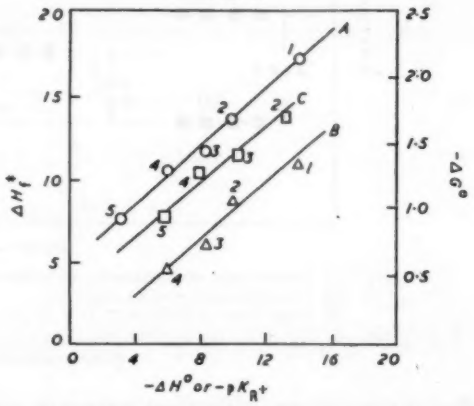


FIG. 4. *Relationships involving* k_t. *Plots of its logarithm at* 33·8° *against* (*A*) $\log_{10}$ (k_m = *relative monomer reactivity, that of styrene being taken as unity* [5]) *and* (*B*) $\log_{10}$ (k_{rel} = *relative rate constant of ethanolysis of substituted diphenylmethyl chloride at* 25°, *that of diphenylmethyl chloride being taken as unity* [6]).

Number	1	2	3	4
Substituent	*p*-Br	Unsubstituted	Di-*p*-Me	*p*-MeO

FIG. 5. *Relationships between the thermodynamic constants.*

A, $-\Delta G°$ (kcal. mole^{-1}) against $-\Delta H°$ (kcal. mole^{-1}); *B*, $\Delta H_t^{\ddagger}$ (kcal. mole^{-1}) against $-\Delta H°$ (kcal. mole^{-1}) (when reaction 2*a* is rate-determining); *C*, $-pK_{R^+}$ against $-\Delta G°$ (kcal. mole^{-1}).

Number	1	2	3	4	5
Substituent	*p*-Br	Unsubstituted	Di-*p*-Me	*p*-MeO	Di-*p*-MeO

5. *Relation to Other Reactions.*—The sequence which we obtain for the effect of *para*-substituents on the rate of dimerisation is the same as that obtained (*a*) for the relative reactivities of substituted styrenes,[6] and (*b*) for the relative rates of solvolysis of substituted diphenylmethyl chlorides [7] (see Fig. 4). As regards the equilibrium $2M \rightleftharpoons D$, the plots of $-\Delta G°$ against $-\Delta H°$, and of $-\Delta H°$ against $\Delta H_t^{\ddagger}$, are straight lines (Fig. 5). $\Delta G°$ also varies linearly with pK_{R^+} for substituted diphenylmethyl alcohols in sulphuric acid [8] (Fig. 5).

[6] Pepper, *Quart. Rev.*, 1954, **8**, 89.
[7] Altscher, Baltzly, and Blackman, *J. Amer. Chem. Soc.*, 1952, **74**, 3649.
[8] Deno, Janizelski, and Schreiskeine, *J. Org. Chem.*, 1954, **19**, 155; *J. Amer. Chem. Soc.*, 1955, **77**, 3044.

6. *Effect of* ortho-*Substituents.*—The fact that neither 1 : 1-di-*o*-tolylethylene nor 1 : 1-di-*o*-methoxyphenylethylene dimerises in benzene–trichloroacetic acid, whereas all the *para*-substituted 1 : 1-diphenylethylenes [1b,8] and the *meta–para*-disubstituted olefins [9,10] dimerise readily, is, we believe, due to steric hindrance. The dimer of 1 : 1-diphenylethylene, 1 : 1 : 3 : 3-tetraphenylbut-1-ene is so highly strained that further addition of monomer is not possible. *para*-Substituents will not affect the steric strain in the dimer since they point away from the cramped parts of the molecule, but *ortho*-substituents will increase the steric strain in the dimer, and we believe that in the 1 : 1-di-*o*-methyl- and 1 : 1-di-*o*-methoxy-compounds this strain prevents the formation of the dimer.

One of us (P. M. S. J.) thanks the D.S.I.R. for a Maintenance Allowance.

UNIVERSITY COLLEGE,
CATHAYS PARK, CARDIFF. [*Received, May 14th*, 1958.]

[9] Schmitz-Dumont, Thömke, and Diebold, *Ber.*, 1937, **70**, 175.
[10] Wolf, *J. Amer. Chem. Soc.*, 1953, **75**, 2673.

---

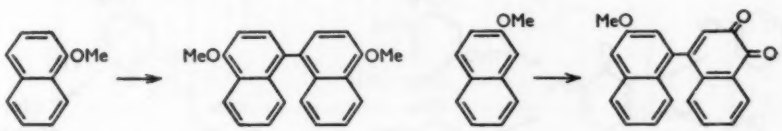
921. *The Oxidation of Phenolic Ethers with Peroxyacetic Acid.*

By H. DAVIDGE, ALWYN G. DAVIES, J. KENYON, and R. F. MASON.

The oxidation of a number of alkyl-, halogeno-, and nitro-substituted alkyl aryl ethers has been examined. Electrophilic 1 : 4-dihydroxylation, usually with the displacement of a hydrogen atom and a methoxyl group, leads to the formation of 1 : 4-quinones. The 1 : 2-quinones formed by 1 : 2-hydroxylation are rapidly oxidised further, with opening of the aromatic ring, giving water-soluble products.

PHENOLS react with hydrogen peroxide and acetic acid, undergoing hydroxylation at positions activated towards electrophilic attack. Further oxidation gives 1 : 4-quinones and ring-fission products such as muconic and fumaric acids.[1]

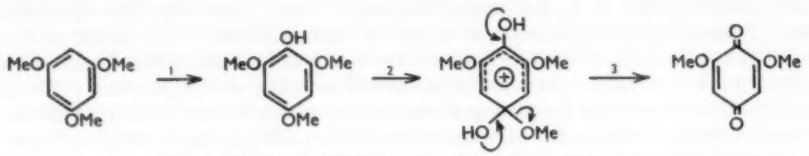
Fernholz [2] showed that a series of alkyl phenyl ethers were oxidised by peroxybenzoic acid, absorbing 0·5—7·8 atom of oxygen, whilst 1- and 2-naphthyl ethers, in benzene, gave first 1 : 2-naphthaquinone, which then reacted with fission of the $C_{(1)}$–$C_{(2)}$ bond to give, *via* the acid anhydride, a monoether of *o*-carboxycinnamic acid. As by-products, the 1- and 2- ethers gave respectively 1 : 4-naphthaquinone and 2-alkoxy-1 : 4-naphthaquinone. The products with peroxyformic acid, however, were quite different: [3]



Friess, Soloway, Morse, and Ingersoll [4] studied the action of peroxybenzoic acid in chloroform on the methyl ethers of mono-, di-, and tri-hydric phenols. 1 : 4-Quinones were usually isolated, sometimes with the displacement of a methoxy-group. 1 : 2-Dimethoxybenzene gave dimethyl muconate only, and in other cases small amounts of oxalic acid derivatives were isolated with the quinones. The relative reactivity and position of quinone-formation were compatible with electrophilic attack upon the ring, and from a

[1] Henderson and Boyd, *J.*, 1910, **97**, 1659; Böeseken and Engelberts, *Proc. Acad. Sci. Amsterdam*, 1931, **34**, 1282; 1932, **35**, 750; Grundman and Trischmann, *Ber.*, 1936, **69**, 1775; Elvidge, Linstead, and Sims, *J.*, 1951, 3386.
[2] Fernholz, *Chem. Ber.*, 1951, **84**, 110.
[3] Fernholz and Piazolo, *Ber.*, 1954, **87**, 578.
[4] Friess, Soloway, Morse, and Ingersoll, *J. Amer. Chem. Soc.*, 1952, **74**, 1305.

kinetic study of the reaction of 1 : 3 : 5-trimethoxybenzene the following mechanism was suggested.



1: $Ph{\cdot}CO_3H$, slow. 2: $Ph{\cdot}CO_3H$, fast. 3: $-MeOH, -H^+$.

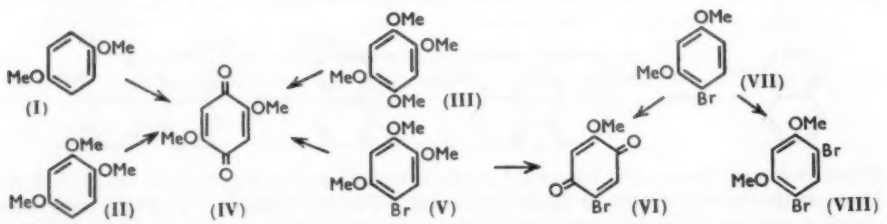
The present investigation was undertaken after it had been observed that the reaction of *p*-tolyl 2 : 4 : 6-trimethoxyphenyl sulphide with hydrogen peroxide in acetic acid gave, not the expected sulphone, but 2 : 6-dimethoxy-1 : 4-benzoquinone which was also obtained by the oxidation of 2 : 4 : 6-trimethoxydiphenylmethanol and of 1 : 3 : 5-trimethoxybenzene.[5]

A number of alkyl-, halogeno-, and nitro-substituted phenolic ethers were prepared and their products of nuclear oxidation examined.

The ether in acetic acid containing a trace of sulphuric acid was mixed with hydrogen peroxide (usually 90%). The ethers which were essentially unchanged after at least a week, or which underwent ring-fission yielding water-soluble substances, are recorded in the Experimental section. When quinones were formed the reactants and products are recorded in Table 1: new quinones were characterised by the derivatives formed on reductive acetylation (Table 2).

The ethers which did not react are those which would be expected to be less susceptible to electrophilic substitution. When oxidation did take place, only 1 : 4-quinones, never 1 : 2-, were isolated, the oxygen atoms being introduced at positions which would be expected to be susceptible to electrophilic attack. The ethers which yielded water-soluble products are again those carrying a number of electron-repelling substituents: a decrease in the concentration of the hydrogen peroxide reduced the proportion of the ether which reacted, but in no case did it permit the isolation of quinone.

Formation of Quinones.—The 1 : 4-quinones were isolated in yields of 10—30%. Usually a hydrogen atom and a methoxyl group, but occasionally two hydrogen atoms, or two methoxyl groups, were eliminated. Thus 1 : 4-dimethoxybenzene (I), 1 : 2 : 4-trimethoxybenzene (II), and 1 : 2 : 4 : 5-tetramethoxybenzene (III) all gave 2 : 5-dimethoxy-1 : 4-benzoquinone (IV).



Alkyl and halogeno-groups were not usually displaced during quinone-formation, but 1-bromo-2 : 4 : 5-trimethoxybenzene (V) was oxidised to a mixture of 2 : 5-dimethoxy-1 : 4-benzoquinone (IV) and 2-bromo-5-methoxy-1 : 4-benzoquinone (VI). In two cases, however, quinone was formed in parallel with a bromine-transfer reaction. 1-Bromo-2 : 4-dimethoxybenzene (VII) in acetic acid containing 30% (100 vol.) hydrogen peroxide, after a few days deposited a mixture of 2-bromo-5-methoxy-1 : 4-benzoquinone (VI) and 1 : 5-dibromo-2 : 4-dimethoxybenzene (VIII), both of which were stable towards the reagents

[5] Kenyon and Mason, *J.*, 1952, 4964.

TABLE 1. *Oxidation of ethers to quinones.*

Ether	Quinone produced			Found (%)				Required (%)			
Substituents in benzene ring, or full name	Substituents in 1 : 4-benzoquinone, or full name	Appearance	M. p.	C	H	Cl/Br/ N	Formula	C	H	Cl/Br/ N	Ref.
1-Methoxy-3 : 5-dimethyl-	2 : 6-Dimethyl- (*A*)	Golden rods	72°	—	—	—	—	—	—	—	1
1 : 2-Dimethoxy-4-methyl-	2-Methoxy-5-methyl- (*B*)	Yellow rods	175—176	63·5	5·2	—	$C_8H_8O_3$	63·2	5·3	—	2
2 : 3-Dimethoxynaphthalene	2 : 3-Dimethoxy-1 : 4-naphthaquinone	Yellow needles	116—117	66·0	4·7	—	$C_{12}H_{10}O_4$	66·0	4·6	—	3
1 : 3-Dimethoxy-	2-Methoxy-5-(4-methoxy-2 : 5-benzoquinonyl)- (*C*)	Yellow rods	231—232 *[a]	61·4	3·9	—	$C_{14}H_{10}O_6$	61·3	3·7	—	
1 : 3-Dibenzyloxy-	2-Benzyloxy-5-(4-benzyloxy-2 : 5-benzoquinonyl)-	Orange rods	258 *	72·9	4·3	—	$C_{26}H_{18}O_6$	73·2	4·3	—	
1 : 3-Dimethoxy-5-methyl-	2-Methoxy-6-methyl-	Yellow plates	149—150·5	62·9	5·1	—	$C_8H_8O_3$	63·2	5·3	—	4
2 : 4-Dimethoxy-1-ethyl-	2-Ethyl-5-methoxy- (*D*)	Yellow needles	154—155	65·2	6·0	—	$C_9H_{10}O_3$	65·1	6·1	—	
1 : 3-Dimethoxynaphthalene	2-Methoxy-1 : 4-naphthaquinone (*E*)	Yellow needles	183—184	70·0	4·4	—	$C_{11}H_8O_3$	70·2	4·3	—	5
1 : 4-Dimethoxy-	2 : 5-Dimethoxy- (*F*)	Yellow leaflets	300 *	56·9	4·7	—	$C_8H_8O_4$	57·2	4·8	—	6
1 : 4-Dimethoxy-2 : 5-dimethyl-	2 : 5-Dimethyl-	Golden rods	125—126 [b]	—	—	—	—	—	—	—	
1-Methoxy-4-*p*-nitrobenzyloxy-	2-Methoxy-5-*p*-nitrobenzyloxy-	Yellow needles	252—255 *	58·4	4·3	5·0	$C_{14}H_{11}O_6N$	58·1	3·8	4·8	
1 : 2 : 3-Trimethoxy-	2 : 6-Dimethoxy-	Orange rods	252 *[a,c]	—	—	—	—	—	—	—	
1 : 3 : 5-Trimethoxy-	2 : 6-Dimethoxy-	Orange rods	252 *[a,c]	—	—	—	—	—	—	—	
1 : 2 : 4-Trimethoxy-	2 : 5-Dimethoxy- (*G*)	Orange rods	300 *	57·4	4·8	—	$C_8H_8O_4$	57·1	4·8	—	
1 : 2 : 4 : 5-Tetramethoxy-	2 : 5-Dimethoxy- (*H*)	Yellow plates	300 *	—	—	—	—	—	—	—	
1-Bromo-2 : 4-dimethoxy-	2-Bromo-5-methoxy- (*I*)	Yellow rods	190—191	39·1	2·5	36·4	$C_7H_5O_3Br$	38·7	2·3	36·8	
1-Chloro-2 : 4-dimethoxy-	2-Chloro-5-methoxy- (*J*)	Yellow needles	174	49·2	3·0	20·9	$C_7H_5O_3Cl$	48·6	2·9	20·6	
2(or 4)-Bromo-1 : 3-dimethoxy-5-methyl-	3(or 5)-Bromo-2-methoxy-6-methyl- (*K*)	Yellow needles	150—151	41·5	3·1	34·1	$C_8H_7O_3Br$	41·6	3·1	34·6	
2 : 4-Dibromo-1 : 3 : 5-trimethoxy-	2 : 6-Dibromo-3 : 5-dimethoxy-[d]	Orange plates	176—177	29·5	1·9	49·0	$C_8H_6O_4Br_2$	29·8	2·1	49·0	7
1-Bromo-2 : 4 : 5-trimethoxy-	2 : 5-Dimethoxy- (*L*)	Golden blades	300 *	57·3	4·7	—	$C_8H_8O_4$	57·2	4·8	—	
	2-Bromo-5-methoxy-	Yellow rods	189—191 *[a]	—	—	—	—	—	—	—	
2-Bromo-1 : 3 : 5-trimethoxy-	3-Bromo-2 : 6-dimethoxy-	Yellow needles	148—149	39·2	2·8	32·1	$C_8H_7O_4Br$	38·9	2·9	32·3	8
2 : 4-Dichloro-1 : 3 : 5-trimethoxy-	2 : 6-Dichloro-3 : 5-dimethoxy-[f]	Golden rods	149—150	41·0	2·7	29·1	$C_8H_6O_4Cl_2$	40·5	2·6	29·9	9
2 : 4 : 2′ : 4′-Tetramethoxydiphenyl-	2-Methoxy-5-(4-methoxy-2 : 5-benzoquinonyl)-	Yellow rods	230 [g]	—	—	—	—	—	—	—	

Notes: * With decomp. [a] Sublimes at 150° *in vacuo*. [b] And mixed with an authentic specimen. [c] And in mixture. [d] Together with an equal amount of 1 : 3 : 5-tribromo-2 : 4 : 6-trimethoxybenzene. [e] And mixed with (*I*). [f] Together with about half its weight of 1 : 3 : 5-trichloro-2 : 4 : 6-trimethoxybenzene, m. p. and mixed m. p. 112°. [g] And mixed with *C*.

[1] Nölting and Forel, *Ber.*, 1885, **18**, 2668, give m. p. 73°. [2] Luff, Perkin, and Robinson, *J.*, 1910, **97**, 1131, give m. p. 170—172°. [3] Fieser, *J. Amer. Chem. Soc.*, 1928, **50**, 439, gives m. p. 115°. [4] Heinrich and Nachtigall, *Ber.*, 1903, **36**, 889, give m. p. 147°. [5] Fieser, *J. Amer. Chem. Soc.*, 1926, **48**, 2922, gives m. p. 183·5°. [6] Anslow and Raistrick, *J.*, 1939, 1446, give m. p. 303°, and Friess *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 1305, 220°. By heating with an ethanolic solution of stannous chloride the quinone was converted into 1 : 4-dihydroxy-2 : 5-dimethoxybenzene, m. p. 171—172·5°. Thoms and Schüller, *Arch. Pharm.*, 1907, **245**, 284, give m. p. 170°. [7] Hofmann, *Ber.*, 1878, **11**, 329, gives m. p. 175°. [8] Levine, *J. Amer. Chem. Soc.*, 1926, **48**, 797, gives m. p. 148°.

used. The original monobromo-ether (VII) reacted with more dilute peroxyacetic acid, or with dilute nitric acid, or immediately with free bromine, giving the dibromo-ether (VIII) as the only water-insoluble product, whereas more concentrated peroxy-acid gave only the quinone. It appears that bromination is probably brought about by free bromine which is formed by a ring-cleavage reaction which does not proceed through the 1 : 4-quinone. A similar halogen-transfer reaction occurs during the oxidation of 2 : 4-dibromo- and 2 : 4-dichloro-1 : 3 : 5-trimethoxybenzene, when a mixture of the corresponding 1 : 3 : 5-trihalogeno-2 : 4 : 6-trimethoxybenzene and 2 : 6-dihalogeno-3 : 5-dimethoxy-1 : 4-benzoquinone is formed.

Whereas Friess *et al.*[4] found that peroxybenzoic acid with 1 : 3-dimethoxybenzene gave 2-hydroxy-5-methoxy-1 : 4-benzoquinone, we find that with peroxyacetic acid nuclear coupling occurs to yield 2-methoxy-5-(4-methoxy-2 : 5-benzoquinonyl)-1 : 4-benzoquinone, identical with the product from 2 : 4 : 2′ : 4′-tetramethoxydiphenyl, This is similar to the nuclear coupling observed by Fernholz and Piazolo[3] and may indicate the incursion of a free-radical process, perhaps initiated by traces of metal ions. The reactions leading to quinone-formation can be accommodated in the mechanism described by Friess *et al.*[4] in which electrophilic hydroxylation at a ring atom carrying an OH or OMe group gives a structure which loses H_2O or HOMe forming the quinone carbonyl group. The 1 : 4-quinones so formed are stable under the reaction conditions and can be isolated, but the 1 : 2-quinones are readily oxidised further by a Baeyer–Villiger reaction[6] and are probably the main source of the water-soluble products.

Experimental

The ethers were prepared by appropriate methods; the following are new.

1-*Methoxy*-4-p-*nitrobenzyloxybenzene*.—A solution of *p*-methoxyphenol (2·5 g.), *p*-nitrobenzyl bromide (4·5 g.), and sodium hydrogen carbonate (2·5 g.) in ethanol (50 c.c.) and water (18 c.c.) was heated under reflux for 1 hr., yielding 1-*methoxy*-4-p-*nitrobenzyloxybenzene* (3·4 g.), pale yellow rods (from ethanol), m. p. 90·5—91·5° (Found: C, 64·8; H, 5·0; N, 6·1. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·0; N, 6·2%).

2(*or* 4)-*Bromo*-1 : 3-*dimethoxy*-5-*methylbenzene*.—A solution of orcinol dimethyl ether (25 g.) and *N*-bromosuccinimide (20 g.) in carbon tetrachloride (150 c.c.) was heated on the steam-bath for 10 hr. The resultant *bromo-ether*, b. p. 112—120°/21 mm. (16 g.), separated from methanol in fern-like needles, m. p. 49—50° (Found: C, 46·5; H, 4·7; Br, 34·2. $C_9H_{11}O_2Br$ requires C, 46·8; H, 4·8; Br, 34·6%).

1-*Chloro*-2 : 4-*dimethoxybenzene*.—A solution of 1-chloro-2 : 4-dihydroxybenzene in sodium hydroxide was shaken with dimethyl sulphate, giving the *chloro-ether*, b. p. 238° (Found: C, 61·2; H, 5·7; Cl, 22·2. $C_8H_9O_2Cl$ requires C, 61·3; H, 5·7; Cl, 22·7%).

2 : 4-*Dichloro*-1 : 3 : 5-*trimethoxybenzene*.—Chlorine from potassium permanganate (6·3 g.) and hydrochloric acid was led into 1 : 3 : 5-trimethoxybenzene (8·4 g.) in acetic acid (50 c.c.). The yellow crystals, after being washed with sodium hydroxide, were crystallised from butanol giving 2 : 4-*dichloro*-1 : 3 : 5-*trimethoxybenzene* (6 g.) as glistening plates, m. p. 155° (Found: C, 45·4; H, 4·1; Cl, 29·7. $C_9H_{10}O_3Cl_2$ requires C, 45·6; H, 4·2; Cl, 30·0%).

Oxidation of Phenolic Ethers to Quinones.—General procedure. To a solution of the ether in glacial acetic acid (5—15 parts) containing sulphuric acid (1—4 drops) was added somewhat more than the calculated amount of hydrogen peroxide (generally 90%, but sometimes as low as 30%, depending on the vigour of the reaction) if necessary drop by drop and with external cooling. After several days the separation of yellow crystals of the quinone appeared to be complete; in a few cases dilution with water proved necessary.

Results are given in Table 1 and those obtained by the reductive acetylation of the quinones in Table 2.

1-*Bromo*-2 : 4-*dimethoxybenzene*. The ether (5 g.) in acetic acid (60 c.c.) and hydrogen peroxide (40 c.c. of 30%) after a week had deposited a mixture of colourless and bright red crystals (3 g.). These were separated in two ways: (i) Warming with dilute sodium hydroxide

[6] Hassal, *Organic Reactions*, 1957, **9**, 73.

XUM

dissolved the red quinone leaving the colourless 1 : 5-dibromo-2 : 4-dimethoxybenzene which separates from ethanol in needles, m. p. 142—143° alone or mixed with an authentic specimen. (ii) Extraction with boiling *cyclo*hexane left undissolved 2-bromo-5-methoxy-1 : 4-benzoquinone, rosettes of golden rods, m. p. 190—191° (cf. Tables 2 and 3). The dibromo-derivative and the quinone were produced in the ratio 2 : 1.

TABLE 2. *Reductive acetylation of quinones.*

Reductive acetylation is effected by heating the quinone (1 g.) with acetic anhydride (3 c.c.) and zinc dust (1 g.) and a few drops of pyridine. It converts a 1 : 4-quinone into the corresponding derivative of 1 : 4-diacetoxybenzene; for example, 2 : 6-dimethyl-1 : 4-benzoquinone (*A*) gives 2 : 5-diacetoxy-1 : 3-dimethylbenzene.

		Product of reductive acetylation								
			Found (%)				Required (%)			
Quinone	Appearance	M. p.	C	H	Cl/Br	Formula	C	H	Cl/Br
A	Glassy leaflets	92—93°	65·1	6·2	—	$C_{12}H_{14}O_4$	64·9	6·4	—
B	Prismatic rods	129—130	60·0	6·1	—	$C_{13}H_{16}O_5$	60·4	5·9	—
C	Long rhombs	187—187·5	59·3	5·1	—	$C_{22}H_{22}O_{10}$	59·2	5·0	—
D	Silky needles	112—113	62·3	6·3	—	$C_{13}H_{16}O_5$	61·9	6·4	—
E	Plates	130—131·5°	—	—	—	—	—	—	—
F, *G* *H*, *L*	Glassy rhombs	182·5—183·5	56·5	5·6	—	$C_{13}H_{16}O_7$	56·7	5·6	—
I	Prismatic rods	136—137	44·1	4·1	25·8	$C_{11}H_{11}O_5Br$	43·6	3·7	26·4
J	Rhombs	127	51·5	4·3	13·8	$C_{11}H_{11}O_5Cl$	51·1	4·3	13·7
K	Glassy plates	133—134	45·7	4·4	24·9	$C_{12}H_{13}O_5Br$	45·4	4·1	25·2

° Fieser, *J. Amer. Chem. Soc.*, 1926, **48**, 2922, gives m. p. 129—130°.

From the mother-liquor there were obtained, by dilution and extraction, additional amounts of the dibromo-derivative (0·6 g.) and the quinone (0·3 g.) together with a highly unsaturated, water-soluble oil (2·4 g.) from which no crystalline derivative could be obtained. A few mg. of oxalic acid (as oxaldi-*p*-toluidide, m. p. 270—272° alone or mixed) were isolated.

Nitric acid (5 c.c.) was added to a solution of the bromo-ether (3 g.) in acetic acid (10 c.c.): the resulting green solution, when diluted with water, deposited a greenish solid from which 1 : 5-dibromo-2 : 4-dimethoxybenzene (1·7 g.), but no quinone, was obtained by recrystallisation from ethanol.

Ethers which are non-reactive towards peroxyacetic acid. The following ethers were recovered after treatment with peroxyacetic acid: 1 : 2-dimethoxybenzene, 1-methoxy-2-methylbenzene, 1-methoxy-4-methylbenzene, 1-bromo-4-methoxybenzene, 1-methoxy-4-phenylbenzene, 1-methoxy-3 : 5-dimethylbenzene, 1-bromo-3-methoxy-4-methylbenzene, 1-chloro-3-methoxy-4-methylbenzene, 2-chloro-5-methoxy-1: 3-dimethylbenzene, 1-chloro-2-methoxy-3-phenylbenzene, 2-methoxy-1 : 3-dimethylbenzene, 1-methoxy-4-phenoxybenzene, ?-bromo-1 : 2-dimethoxy-4-methylbenzene, 2-chloro-1 : 4-dimethoxybenzene, 1 : 4-dimethoxy-2-methylbenzene, 1 : 4-dimethoxy-2-phenoxybenzene, 1 : 2-dimethoxy-4-nitrobenzene, 2 : 4-dimethoxy-1-nitrobenzene, 1 : 3-dimethoxy-2-*p*-nitrobenzyloxybenzene, 1 : 4-dimethoxynaphthalene, 1 : 4-diphenoxybenzene, 1 : 2 : 3-tribromo-4 : 5 : 6-trimethoxybenzene, and 4 : 4′-dimethoxydiphenyl ether.

Ethers which are oxidised to water-soluble products. The following ethers gave only water-soluble products after treatment with peroxyacetic acid: methoxybenzene, 1-methoxy-3-methylbenzene, 2-methoxy-1 : 4-dimethylbenzene, 4-methoxy-1 : 2-dimethylbenzene, 1-methoxy-3-hydroxybenzene, 1-methoxy-4-hydroxybenzene, 1 : 4-dimethoxy-2-bromobenzene, 2 : 7-dimethoxynaphthalene, and 1 : 5-dimethoxynaphthalene.

Thanks are expressed to the Central Research Funds Committee of London University for a Grant.

BATTERSEA COLLEGE OF TECHNOLOGY, LONDON, S.W.11.
BRITISH OXYGEN RESEARCH AND DEVELOPMENT LTD.,
DEER PARK ROAD, LONDON, S.W.19.

[*Received, August 8th*, 1958.]

XUM

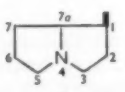
922. *The* Senecio *Alkaloids. Part XIII.* The Absolute Configuration of Heliotridane (1-Methylpyrrolizidine) and the "Necine" Bases.*

By F. L. Warren and M. E. von Klemperer.

Heliothidane is converted by three successive Hofmann reactions into (+)-3-methylheptane, from which the absolute configuration of heliotridane, and hence the "necine" bases, is deduced.

The several "necine" bases, which are hydroxylated 1-methylpyrrolizidines, have been extensively studied and assigned relative configurations at their asymmetric centres.[1] Leonard [2] has recently deduced an absolute configuration on the basis of a correlation between the molecular-rotational shifts of *iso*retronecanol and (−)-lupinine, the structure of the latter being fully defined by Cookson [3] on the basis of the degradation by Karrer and his co-workers to (−)-4-methylnonane.[4]

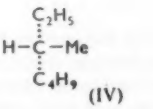
We have now degraded heliotridane (I) to (+)-3-methylheptane which is assigned configuration (IV) (*D* on Klyne's symbolism,[5] *S* on that of Cahn, Ingold, and Prelog [6]), and have so established conclusively, but contrary to the deductions from molecular rotational shifts,[2] that the orientation of heliotridane at position 1 is *S* (Cahn, Ingold, and Prelog's symbolism [6]).



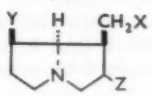
(I)

$C_3H_7 \cdot CH(NMe_2) \cdot CHMe \cdot C_2H_5$ (II)

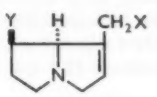
$C_2H_5 \cdot CH{=}CH \cdot CHMe \cdot C_2H_5$ (III)



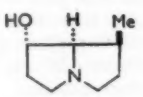
(IV)



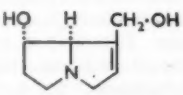
	X	Y	Z
(I) Heliotridane	H	H	H
(V) Platynecine	OH	OH	H
(VI) Retronecanol	H	OH	H
(VII) *iso*Retronecanol	OH	H	H
(VIII) Rosmarinecine	OH	OH	OH



	X	Y
(IX) Retronecine	OH	OH
(X) Deoxyretronecine	H	OH
(XI) Supinidine	OH	H



(XII) Oxyheliotridane



(XIII) Heliotridine

Heliotridane (I) has been obtained by several methods but the preparation from readily available material was best carried out by the following procedure. Retrorsine or isatidine was catalytically hydrogenolysed and then further hydrolysed to retronecanol [7,8] which was dehydrated with sulphuric acid and reduced in the presence of platinum to heliotridane (I).[9] This was submitted to two successive Hofmann degradations with

* Part XII, *J.*, 1955, 65.

[1] Cf. Warren, *Progress Chem. Org. Natural Products*, 1955, **12**, 198; Adams and Gianturco, *Angew. Chem.*, 1957, **69**, 5.
[2] Leonard, *Chem. and Ind.*, 1957, 1455.
[3] Cookson, *ibid.*, 1953, 337.
[4] Karrer, Canal, Zohner, and Widner, *Helv. Chim. Acta*, 1928, **11**, 1062.
[5] Klyne, "Progress in Stereochemistry," Butterworths, London, 1954, p. 205.
[6] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 85.
[7] Barger, Seshadri, Watt, and Yabuta, *J.*, 1935, 11.
[8] Leisegang and Warren, *J.*, 1949, 486.
[9] Konawolowa and Orékhoff, *Bull. Soc. chim. France*, 1937, 1285; cf. Adams and Rogers, *J. Amer. Chem. Soc.*, 1941, **63**, 228.

XUM

reduction at each stage as described by Men'shikov [10] to give 4-dimethylamino-3-methylheptane (II). This amine (II) has now been converted into its methiodide which by a third Hofmann reaction yielded a hydrocarbon envisaged in accordance with the Hofmann rule [11] as 5-methylhept-3-ene (III). This methylheptene was reduced catalytically to partially racemised (+)-3-methylheptane (IV), $[\alpha]_D$ +4·1°, compared with the value $[\alpha]_D$ +4·6° given by Levene and Marker [12] for their synthetic product or +12·0° for their calculated maximum rotation.

The ready dehydration of platynecine to anhydroplatynecine [13] necessitates that the methyl group in heliotridane must be *trans* to the 7*a*-hydrogen atom,[14] so that Men'shikov's (−)-heliotridane is now (1*S*,7*aS*)-1-methylheliotridane (I).

The absolute configurations of the hydroxy-derivatives of this (1*S*,7*aS*)-1-methylpyrrolizidine pivot on the relative orientation of the hydroxyl groups of platynecine which is fully established by two different methods (Adams and Van Duuren [15] and by these laboratories [16]) and which now becomes (1*S*,7*R*,7*aR*)-1 : 7-bishydroxymethylpyrrolizidine (V). The structures of retronecanol [7] (VI), *iso*retronecanol [17] (VII), rosmarinecine [16,18] (VIII), retronecine [14] (IX), isatinicine (retronecine *N*-oxide),[8] deoxyretronecine [8] (X), and supinidine [19] (XI) follow logically from their structural relations with platynecine. The change in the orientation of the 7-hydroxyl group of retronecanol and retrorsine then gives oxyheliotridane [17] (XII) and heliotridine [17] (XIII) respectively.

Experimental

4-Dimethylamino-3-methylheptane.—Heliotridane, b. p. 166°/700 mm., d_4^{16} 0·940, $[\alpha]_D^{16}$ −111° (pure liquid) (Adams and Rogers [20] give b. p. 165—166°, d_4^{24} 0·911, $[\alpha]_D^{14}$ −91°), was submitted twice to the Hofmann degradation and reduction of the product at each stage as described by Men'shikov,[10] to give 4-dimethylamino-3-methylheptane, b. p. 180°/700 mm., $[\alpha]_D^{20}$ −0·59° (pure liquid), d_4^{20} 0·948 (Found: C, 76·4; H, 14·5. Calc. for $C_{10}H_{23}N$: C, 76·35; H, 14·7%). Men'shikov [10] gives b. p. 180—181°.

The tertiary base (8 g.) in acetone (20 ml.) was treated slowly with methyl iodide (5 ml., 1·5 mol.) in acetone (10 ml.). The product crystallised from acetone, to give the *methiodide*, m. p. 184°, $[\alpha]_D^{26}$ +5·9° (*c* 1 in ethanol) (Found: C, 44·0; H, 8·9. $C_{11}H_{26}NI$ requires C, 44·1; H, 8·7%).

3-Methylheptane.—The methiodide (16 g.) in water was stirred for 12 hr. with silver oxide, prepared from silver nitrate (9 g.). The solution was evaporated to dryness under reduced pressure at 40°, and then at 130°/20 mm. with a cold trap at −70°. The distillate was taken up in ether, and the solution washed, dried, and distilled, to give 5-methylhept-3-ene (1·35 g.), b. p. 110—120°, $[\alpha]_D^{20\cdot5}$ −1·7° (*c* 18 in methanol).

5-Methylhept-3-ene (1·0 g.) in methanol in the presence of platinum oxide absorbed 200 ml. of hydrogen in 20 min. The product was poured into water, taken up in ether, washed and evaporated through a fractionating column. The product distilled at 110—115° to a colourless liquid, d_4^{19} 0·720, $[\alpha]_D^{20\cdot5}$ +4·1° (Found: C, 84·6; H, 15·8. Calc. for C_8H_{18}: C, 84·1; H, 15·9%). Levene and Marker [12] give d_4^{22} 0·710, $[\alpha]_D^{22}$ +4·55°.

The authors gratefully acknowledge grants to assist this work from the South African Council for Scientific and Industrial Research and from African Explosives and Chemical Industries.

Department of Chemistry and Chemical Engineering, University of Natal, Pietermaritzburg, South Africa. [*Received, June 16th*, 1958.]

[10] Men'shikov, *Ber.*, 1935, **68**, 1555; *Bull. Acad. Sci. U.R.S.S. Ser. Chim.*, 1937, 1035 (*Brit. Abs.*, AII, 1938, 162).
[11] Hanhart and Ingold, *J.*, 1927, 997.
[12] Levene and Marker, *J. Biol. Chem.*, 1931, **91**, 763.
[13] Konowalowa and Orechoff, *Ber.*, 1935, **69**, 1908.
[14] Leonard and Felly, *J. Amer. Chem. Soc.*, 1950, **72**, 2537; cf. refs.
[15] Adams and Van Duuren, *J. Amer. Chem. Soc.*, 1954, **76**, 6379.
[16] Dry, Koekemoer, and Warren, *J.*, 1955, 59.
[17] Men'shikov and Kurzokov, *J. Gen. Chem. U.R.S.S.*, 1949, **19**, 1702.
[18] Richardson and Warren, *J.*, 1943, 452.
[19] Men'shikov and Gurevich, *J. Gen. Chem. U.R.S.S.*, 1949, **19**, 1382.
[20] Adams and Rogers, *J. Amer. Chem. Soc.*, 1941, **63**, 234.

923. *Studies in Relation to Biosynthesis. Part XVII.* Sclerotiorin, Citrinin, and Citromycetin.*

By A. J. Birch, P. Fitton, E. Pride, A. J. Ryan, Herchel Smith, and W. B. Whalley.

The routes of biosynthesis, in appropriate moulds, of the substances named in the title have been examined by means of feeding experiments with ^{14}C-labelled acetic and formic acids.

Some previous papers [1] dealt with a speculative examination of the biosynthetic origins of plant and mould products from acetic acid by head-to-tail linkage, or from acetic acid and methionine. These predictions have been confirmed by direct experiment with $CH_3{\cdot}^{14}CO_2H$ in two cases [2,3] where the molecule can arise from a straight chain of acetic acid units joined by head-to-tail linkage, and in one case (mycophenolic acid) [4,5] where methionine is also involved. We have now extended our researches to trace the origins of molecules which can only arise from *branched* carbon chains. From previous work there seem to be three likely modes of origin: (A) From acetic acid, by head-to-tail linkage in a straight chain with the introduction of C_1 units from the C_1 pool (choline, methionine etc.). (B) From acetic acid by production of branched chains employing head-to-tail linkage. (C) By the isoprene route formally similar to (B) but with a definite intermediate in the form of mevalonic acid.

Mycophenolic acid [4,5] is an interesting example of the working of routes (A) and (C) in one compound; no example of route (B) had, before the present work, been demonstrated. It cannot be excluded that *intermediates* in the production of griseofulvin or methylsalicylic acid, or any other compound involving the orcinol-type (aldol) of ring-closure, could be branched in the manner of route (B) but in the absence of experimental evidence no such intermediates need at present be postulated.

Sclerotiorin.—When the probable formula [6] (I) is considered the most likely route to sclerotiorin is of type (A) with three introduced methyl groups (or four if the carbon of the methinyloxy-group is derived from the C_1 pool). The " extra " acetic acid unit may also involve a branched main chain, but in view of the slight uncertainty in the structure we have confined ourselves to confirming its origin from acetic acid.

Sclerotiorin was produced from *Penicillium multicolor* in media containing, in separate experiments, $CH_3{\cdot}^{14}CO_2H$, $H{\cdot}^{14}CO_2H$, and $^{14}CH_3{\cdot}CO_2H$, the radioactivity being incorporated into the metabolite to the extent of 3, 20, and 8% respectively. The products were hydrolysed by alkali to 4 : 6-dimethylocta-1 : 4-dienoic acid (II) which was oxidised [8] to 2-methylbutanal (III) (examined as the 2 : 4-dinitrophenylhydrazone). The sclerotiorin and the 2-methylbutanal derivatives were subjected to Kuhn–Roth oxidation and the labelling in the resultant acetic acid was examined by pyrolysis of the lithium salt.[9] The results, set out in our usual fashion in Scheme 1, confirm the applicability of route (A) in showing the expected origin of sclerotiorin from nine molecules of acetic acid and three C_1 units.

The radioactive assay data (see Experimental section) are in quantitative agreement with the postulated distributions of radioactivity shown in (Ia), (Ib), and (Ic) in material

* Part XVI, *J.*, 1958, 2622.

[1] Birch and Donovan, *Austral. J. Chem.*, 1953, **6**, 360; Birch, Elliott, and Penfold, *ibid.*, 1954, **7**, 169; Birch, *Fortschr. Chem. org. Naturstoffe*, 1957, **16**, 186.
[2] Birch, Massy-Westropp, and Moye, *Austral. J. Chem.*, 1958, **8**, 539.
[3] Birch, Massy-Westropp, Rickards, and Smith, *J.*, 1958, 360.
[4] Birch, English, Massy-Westropp, Slaytor, and Smith, *J.*, 1958, 365.
[5] Birch, English, Massy-Westropp, and Smith, *ibid.*, p. 369.
[6] Fielding, Robertson, Travers, and Whalley, *J.*, 1958, 1814.
[7] Watanabe, *J. Pharm. Soc. Japan*, 1952, **72**, 807.
[8] Eade, Page, Robertson, Turner, and Whalley, *J.*, 1957, 4920.
[9] Cornforth, Hunter, and Popjak, *Biochem. J.*, 1953, **54**, 597.

XUM

derived from $CH_3 \cdot {}^{14}CO_2H$, $H \cdot {}^{14}CO_2H$, and ${}^{14}CH_3 \cdot CO_2H$, respectively. Further features of interest to emerge are:

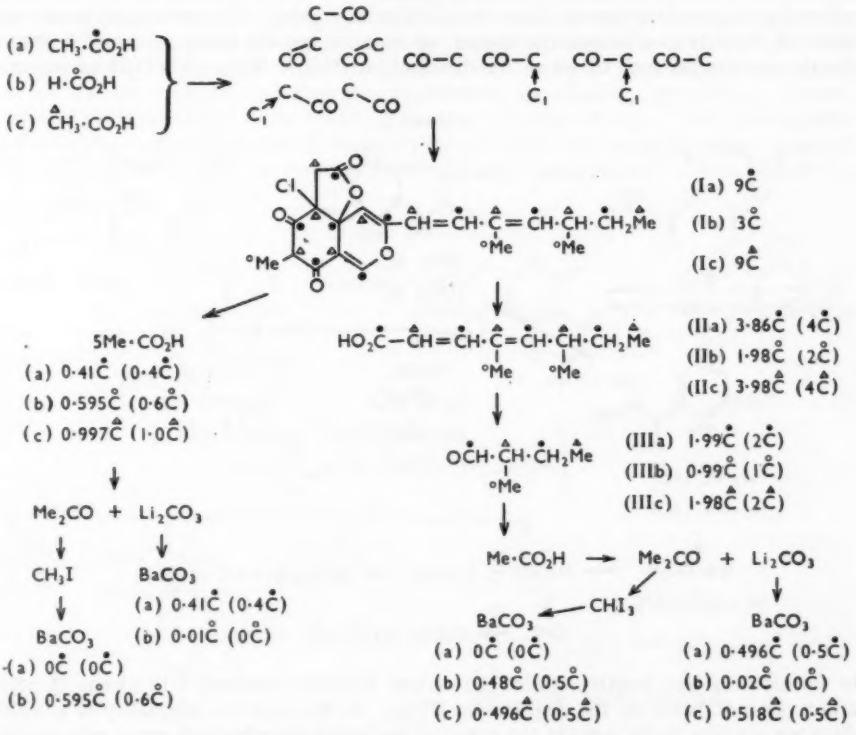
(i) The results of the Kuhn–Roth oxidations of sclerotiorin are consistent with the remaining degradations only if the production of *five* acetic acid units (in 90% yield) be assumed; *i.e.*, one arises from the "extra" acetic acid unit in the lactone ring which appears to be labelled to the same extent as those in the main chain.

(ii) The carbon of the methinyloxy-group must come from a reduced carboxyl group of acetic acid.

(iii) During the biosynthesis from ${}^{14}CH_3 \cdot CO_2H$ there is no appreciable redistribution of activity between the methyl- and the carboxyl-carbon atom, and no appreciable conversion into $H \cdot {}^{14}CO_2H$ or a biological equivalent.

(iv) The introduced methyl groups in the aliphatic side-chain are labelled to the same extent as that attached to the *cyclo*hexane-1 : 3-dione ring.

Scheme 1.



When the dienoic acid (II) labelled in the 4- and the 6-methyl group was added to the growth medium of *P. multicolor*, radioactive sclerotiorin was obtained and on degradation gave the dienoic acid (II) which was found to contain four-ninths of the activity of the precursor sclerotiorin. This result is consistent with the degradation of the acid (II) to ${}^{14}CH_3 \cdot CO_2H$ before incorporation and may be taken as evidence that this acid is not an intermediate in the biosynthesis.

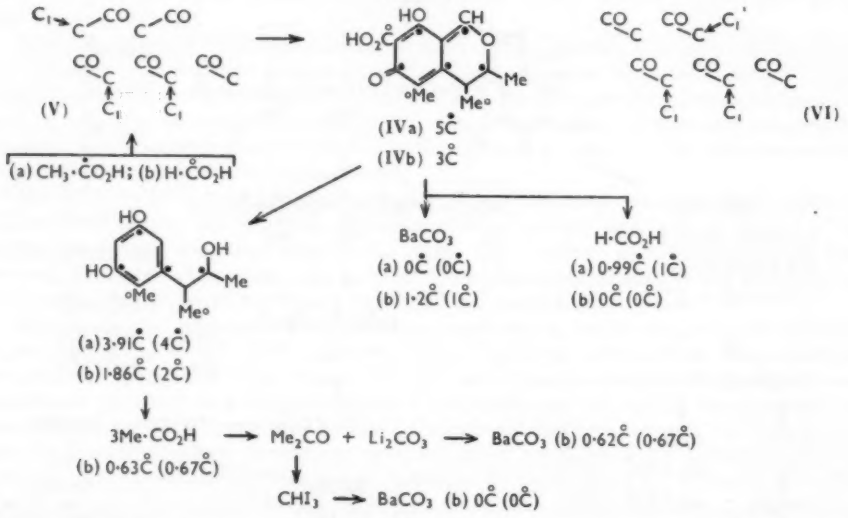
It is notable that in the present case, as with ergosterol,[10] introduced C_1 units are found

[10] Alexander, Gold, and Schwenk, *J. Amer. Chem. Soc.*, 1957, **79**, 2967; Alexander and Schwenk, *ibid.*, p. 4554.

in an aliphatic chain. This is of particular interest in view of the postulated biogenesis [4] of the macrolide antibiotics where methyl groups are similarly thought to be introduced into non-aromatic systems derived by head-to-tail linkage of acetic acid units.

Citrinin.—This substance [11] (IV) could arise from five acetic acid units and three C_1 units but it is not possible to decide from the formula whether the C_1 units comprise the two methyl groups and the carboxyl group introduced into a straight acetic-acid-derived chain as in (V), or whether the two methyl groups and the methinyloxy-group are introduced into a branched acetic-acid-derived chain, *e.g.*, as in (VI). Other less probable biosyntheses could be envisaged. In fact, feeding experiments with $CH_3{\cdot}^{14}CO_2H$ and $H{\cdot}^{14}CO_2H$ confirm the former route (V) in *Aspergillus candidus*. Its is particularly striking that the incorporation of radioactivity into citrinin with $H{\cdot}^{14}CO_2H$ as substrate is at least 66%: that from $CH_3{\cdot}^{14}CO_2H$ is lower (11%) but still high for acetate incorporation. The postulated distributions of radioactivity from $H{\cdot}^{14}CO_2H$ and $CH_3{\cdot}^{14}CO_2H$ are shown in the formulæ (IVa) and (IVb). They were confirmed by the degradations outlined in Scheme 2. The acid hydrolysis [12] of the labelled citrinins to carbon dioxide (from the carboxyl group) and formic acid (from the methinyloxy-group) was particularly instructive. With $CH_3{\cdot}^{14}CO_2H$ as substrate the former was inactive but the latter contained 0·99 atom of active carbon per mol. based on the distribution (IVa). With $H{\cdot}^{14}CO_2H$ as substrate

Scheme 2.



the formic acid was inactive whilst the carbon dioxide contained 1·12 atoms of active carbon per mol. based on the distribution (IVb). In this case the inequality of labelling, which we consider to be outside the range of our usual experimental error, may imply a sequential rather than a simultaneous addition of C_1 units. In this biosynthesis, as with that of sclerotiorin, a notable step is the reduction of an acetic-acid carboxyl group to a lower oxidation state. Since this work was completed Dr. E. Schwenk (Worcester Foundation) has informed us of similar independent work arriving at the same conclusions: this is being published elsewhere.

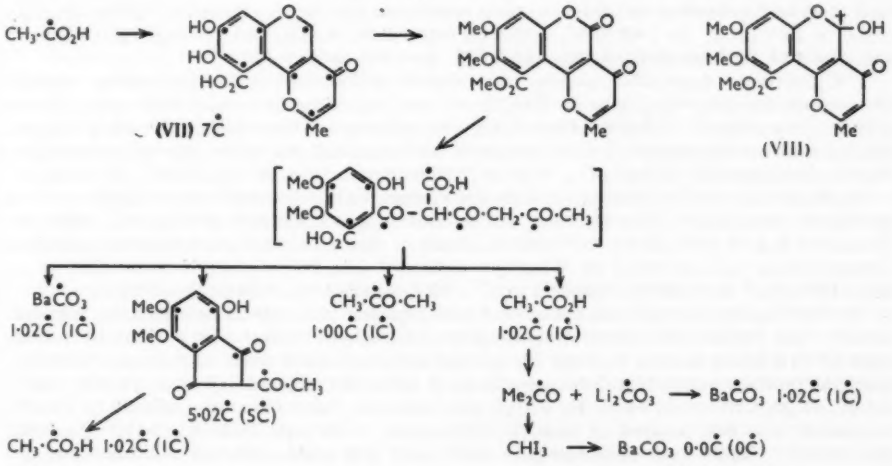
Citromycetin.—Attention has been drawn to the fact that citromycetin [13] (VII), fulvic

[11] Brown, Cartwright, Robertson, and Whalley, *J.*, 1949, 867.
[12] *Idem, ibid.*, p. 859.
[13] Robertson, Whalley, and Yates, *J.*, 1951, 2013.

acid, and fusarubin can all be derived from the same skeleton containing a branch involving one carbon atom [14] which we believed [4] to arise from the introduction of a C_1 unit in an acetate-derived chain. Earlier, however, Birch and Donovan had noted the possibility that fusarubin could be derived from a straight acetic acid chain.[14b] Feeding experiments with *P. frequentans* using $CH_3{\cdot}{}^{14}CO_2H$ and $H{\cdot}{}^{14}CO_2H$ have shown that in citromycetin the carbon skeleton is entirely derived from acetic acid. Our first indication of this was that, whereas activity from $CH_3{\cdot}{}^{14}CO_2H$ was incorporated into citromycetin to an expected extent (*ca.* 2%), only 0·8% of the activity of the added $H{\cdot}{}^{14}CO_2H$ was so recovered, an incorporation far lower than that so far encountered with any substance which incorporates C_1 units.

The degradations illustrated in Scheme 3 conclusively show the presence of seven almost equally labelled carbon atoms in the citromycetin derived from $CH_3{\cdot}{}^{14}CO_2H$, and it is notable that the activity of the branch carbon atom is the same as that of the labelled carbon atoms in the main chain. The explanation of the results cannot therefore be merely that the formic acid is not biologically activated for incorporation. Degradation of the material derived from $H{\cdot}{}^{14}CO_2H$ indicated a small general distribution of radioactivity. Thus the carbon dioxide obtained by decarboxylation of citromycetin to citromycin contained 13% of the total activity and the acetone (representing three carbon atoms of the main chain) and formic acid obtained by alkaline degradation of citromycetinol (VIII) contained 24 and 0·5% respectively of this activity. Had citromycetin been formed by route (A) then all of the activity from $H{\cdot}{}^{14}CO_2H$ would have been localised on the carbon atom marked † in formula (VIII) and thus recovered in the formic acid above.

Scheme 3.



Experimental

General directions are as for Part XIV.[4] Relative molar activities (r.m.a.'s) (a), (b), and (c) refer to the labelled metabolites and their degradation products derived from $CH_3{\cdot}{}^{14}CO_2H$, $H{\cdot}{}^{14}CO_2H$, and $^{14}CH_3{\cdot}CO_2H$ respectively. Theoretical numbers of carbon atoms in degradation products are based on the appropriate postulated distributions in the labelled metabolites. Samples of barium carbonate denoted (Me) or (CO_2H) are from the methyl and the carboxyl groups respectively of acetic acid produced by Kuhn–Roth oxidation.

[14] (*a*) Dean, Eade, Mombasher, and Robertson, *Nature*, 1957, **179**, 366; (*b*) Birch and Donovan, *Chem. and Ind.*, 1954, 1047.

[^{14}C]*Sclerotiorin.*—*P. multicolor* Grigorieva-Manoilova and Poradielova was cultured as described earlier [15] except that on the tenth day labelled sodium formate or sodium acetate (0·1—0·4 mc) in water was distributed equally between three flasks (750 c.c. of culture medium per flask) under aseptic conditions. After a further 5 days the cultures were harvested in the usual manner. After a preliminary purification by crystallisation from methanol the crude sclerotiorin was diluted with inactive material and brought to radiochemical purity by a combination of processes involving further crystallisations from methanol, percolation in benzene through a column of Florisil and high-vacuum sublimation [Found: r.m.a. $\times 10^{-5}$, (a) 4·41; (b) 6·27; (c) 3·28].

Degradations of [^{14}C]*Sclerotiorin.*—(i) The labelled metabolite was hydrolysed with N-sodium hydroxide as previously described.[7] The resulting 4 : 5-dimethylocta-2 : 4-dienoic acid was purified by recrystallisation from 50% aqueous methanol and then by vacuum-sublimation. It had m. p. 91—92° (lit.,[8] m. p. 92°) [Found: r.m.a. $\times 10^{-5}$, (a) 1·89 (4C, 1·96); (b) 4·13 (2C, 4·18); (c) 1·45 (4C, 1·46)].

(ii) Kuhn–Roth oxidation of the labelled sclerotiorin gave acetic acid (isolated as lithium acetate). An aliquot part was converted into the *p*-bromophenacyl ester, m. p. 86—87° [Found: r.m.a. $\times 10^{-5}$, (a) 0·195 (0·4C, 0·196); (b) 1·24 (0·6C, 1·25); (c) 0·363 (1C, 0·364)]. The remainder of the lithium salt was pyrolysed, giving $BaCO_3$(Me) [Found: r.m.a. $\times 10^{-5}$ (a) 0; (b) 1·24 (0·6C, 1·25)] and $BaCO_3(CO_2H)$ [Found: r.m.a. $\times 10^{-5}$, (a) 0·199 (0·4C, 0·196); (b) 0·003].

(iii) The [^{14}C]sclerotiorin was ozonised as previously described.[8] The resultant 2-methylbutanal 2 : 4-dinitrophenylhydrazone was percolated in benzene through bentonite–kieselguhr (1 : 1; 15 g.) and twice recrystallised from methanol. It had m. p. 133—134° and was identical with the derivative from the synthetic (±) aldehyde [Found: r.m.a. $\times 10^{-5}$ (a) 0·976 (2C, 0·980); (b) 2·07 (1C, 2·09); (c) 0·716 (2C, 0·730)].

(iv) The above radioactive 2 : 4-dinitrophenylhydrazone was diluted with synthetic material [Found r.m.a. $\times 10^{-4}$ (a) 2·38; (b) 2·15; (c) 1·98]. Kuhn–Roth oxidation gave acetic acid (1·92 mol.) obtained as lithium acetate which was pyrolysed, giving $BaCO_3$(Me) [Found: r.m.a. $\times 10^{-4}$, (a) 0; (b) 1·02 (0·5C, 1·07); (c) 0·491 (0·5C, 0·495)] and $BaCO_3(CO_2H)$ [Found: r.m.a. $\times 10^{-4}$, (a) 0·590 (0·5C, 0·595); (b) 0·039; (c) 0·513 (0·5C, 0·495)].

[^{14}C]*Citrinin.*—*Aspergillus candidus* was cultured as described by Wyllie [16] except that on the seventh day $CH_3{\cdot}^{14}CO_2Na$ or $H{\cdot}^{14}CO_2Na$ (0·1 mc) was added to each of three culture flasks (750 c.c. of medium). After a further 3 days the citrinin was harvested in the usual fashion, diluted with inactive material, and brought to radiochemical purity by repeated recrystallisation from methanol. It had m. p. 169—171° [Found: r.m.a. $\times 10^{-6}$ (a) 2·727; (b) 1·319].

Degradations of [^{14}C]*Citrinin.*—(i) Labelled citrinin was hydrolysed with sulphuric acid as previously described.[12] The resulting carbon dioxide was converted into barium carbonate [Found: r.m.a. $\times 10^{-6}$, (a) 0; (b) 0·490 (1C, 0·430)]. The formic acid was collected as sodium formate which was converted by Whalley's method [17] into *NN'*-diphenylformamidine, m. p. 188—190° (lit.,[17] m. p. 193°) [Found: r.m.a. $\times 10^{-6}$, (a) 0·541 (1C, 0·545); (b) 0·009].

(ii) Radioactive citrinin was hydrolysed with aqueous ammonia as described by Schwenk *et al.*[18] The crude 5-(2-hydroxy-1-methylpropyl)-4-methylresorcinol was purified by percolation of its solution in ether through Florisil and recrystallisation from chloroform. Obtained thus, the product was a chloroform solvate, m. p. 129—130° (Found: C, 53·9; H, 6·6. Calc. for $2C_{11}H_{16}O_3{,}CHCl_3$: C, 54·0; H, 6·5%), and since the chloroform was difficult to remove completely was best assayed as such [Found: r.m.a. $\times 10^{-6}$, (a) 2·13 (4C, 2·18); (b) 0·815 (2C, 0·879)]. Kuhn–Roth oxidation gave acetic acid (2·25 mol.), collected as lithium acetate. An aliquot part was converted into *p*-bromophenacyl acetate [Found: r.m.a. $\times 10^{-6}$, (b) 0·276 (0·67C, 0·293)]. The remainder was pyrolysed, giving $BaCO_3$(Me) [Found: r.m.a. (b) 0], and $BaCO_3(CO_2H)$ [Found: r.m.a. $\times 10^{-6}$, (b) 0·273 (0·67C, 0·293)].

[^{14}C]*Citromycetin.*—*P. frequentans* Westling L.S.H.T.M. No. Ad. 7 was cultured by Hetherington and Raistrick's method.[19] On the seventh day $CH_3{\cdot}^{14}CO_2Na$ or $H{\cdot}^{14}CO_2Na$ (0·1 mc) was added to each of four flasks and after a further 7 days the citromycetin was

[15] Curtin and Reilly, *Biochem. J.*, 1940, **34**, 1419; 1943, **37**, 36.
[16] Wyllie, *Canad. J. Publ. Health*, 1945, **36**, 477.
[17] Whalley, *J.*, 1948, 1015.
[18] Schwenk, Schubert, and Stahl, *Arch. Biochem. Biophys.*, 1949, **20**, 220.
[19] Hetherington and Raistrick, *Phil. Trans.*, 1931, **220**, *B*, 209.

XUM

isolated. An aliquot part of the material was purified in the usual manner [Found: r.m.a. × 10^{-6}, (a) 1·29; (b) 0·159].

The degradations of both types of labelled material are based on procedures already described.[13, 20]

Degradations of Citromycetin derived from $CH_3 \cdot {}^{14}CO_2Na$.—(i) The labelled citromycetin was decarboxylated and the carbon dioxide converted into barium carbonate (Found: r.m.a., 985).

(ii) The crude citromycetin was converted into di-*O*-methylcitromycetin methyl ester by treatment with ethereal diazomethane. The ester was purified by repeated high-vacuum sublimation. It had m. p. 176—178° (Found: r.m.a. × 10^{-6}, 1·290) and was converted into di-*O*-methylcitromycetinone methyl ester (1·3 g.), m. p. 240° (decomp.) (r.m.a. × 10^{-6}, 1·29), which was degraded with hot aqueous 2N-sodium hydroxide (65 c.c.). The resultant acetone was collected as the 2 : 4-dinitrophenylhydrazone (200 mg.) which was purified by chromatography in chloroform on alumina and by recrystallisation from methanol. It had m. p. 124—126° [Found: r.m.a. × 10^{-6}, 0·184 (1C, 0·184)]. The precipitate from the neutralised and cooled hydrolysate was recrystallised from methanol, to give 2-acetyl-7-hydroxy-4 : 5-dimethoxyindane-1 : 3-dione (310 mg.), m. p. 156°, previously thought to be 3-acetyl-4-hydroxy-6 : 7-dimethoxycoumarin-5-carboxylic acid [Found: r.m.a. × 10^{-6}, 0·926 (5C, 0·922)]. The filtrate was refluxed in a stream of nitrogen for 1 hr. and the effluent gases were trapped in aqueous barium hydroxide. The barium carbonate was washed and dried [Found: r.m.a. × 10^{-6}, 0·187 (1C, 0·184)]. The residual solution was distilled and the acetic acid collected as lithium acetate. An aliquot part was converted into the *p*-bromophenacyl ester which was chromatographed on Florisil in mixtures of light petroleum (b. p. 60—80°) and benzene, and recrystallised twice from light petroleum (b. p. 60—80°). It had m. p. 84—86° [Found: r.m.a. × 10^{-6}, 0·188 (1C, 0·184)]. The residual lithium acetate was pyrolysed, giving $BaCO_3(Me)$ (Found: r.m.a., 0) and $BaCO_3(CO_2H)$ [Found: r.m.a. × 10^{-6}, 0·187 (1C, 0·184)].

(iii) The above indane-1 : 3-dione was fused with potassium hydroxide. The melt was dissolved in water, and the resulting solution was acidified and distilled, to give acetic acid (2·0 mol.) which was collected as lithium acetate and converted into *p*-bromophenacyl acetate, m. p. 84—86° (Found: r.m.a. × 10^{-6}, 0·187 (1C, 0·184)].

Degradations of Citromycetin derived from $H \cdot {}^{14}CO_2H$.—(i) Decarboxylation as above gave barium carbonate (Found: r.m.a. × 10^{-4}, 2·14).

(ii) Di-*O*-methylcitromycetin methyl ester was oxidised with lead tetra-acetate in acetic acid, to give (from methanol) di-*O*-methylcitromycetinol methyl ester (VIII) which we obtained as a *solvate*, m. p. 156—158°. [Robertson *et al.*[13] gave m. p. 234° (decomp.) for the unsolvated material] (Found: C, 57·2; H, 5·8%; r.m.a. × 10^{-4}, 15·8. $C_{17}H_{16}O_8.CH_3 \cdot OH$ requires C, 56·8; H, 5·3%). This ester (200 mg.) was degraded with aqueous sodium hydroxide in a stream of nitrogen. Acetone 2 : 4-dinitrophenylhydrazone (35 mg.) was obtained from the effluent vapours and purified as before. It had m. p. 122—124° (Found: r.m.a. × 10^{-4}, 3·88).

We thank the Rockefeller Foundation (New York) and the Distillers Co. Ltd. for financial support and Imperial Chemical Industries Limited for the loan of equipment. The work was carried out during the tenure of the Sir Clement Royds Memorial Scholarship of the University of Manchester (by P. F.), a D.S.I.R. maintenance grant (by E. P.), and a C.S.I.R.O. Overseas Studentship (by A. J. R.). The culture of *P. multicolor* was obtained through the courtesy of Dr. C. R. Benjamin from the Northern Utilisation Research and Development Division, Peoria, Illinois; the culture of *P. frequentans* was obtained from Mr. G. Smith of the London School of Hygiene and Tropical Medicine; and Drs. H. H. Warren (Williams College, Williamstown, Mass.) and E. S. Wallis (Princeton) provided the culture of *A. candidus*. We thank these gentlemen for their generous co-operation. Cultures were grown by Miss M. Hay.

THE UNIVERSITY, MANCHESTER, 13.
THE UNIVERSITY, LIVERPOOL.

[*Received, June 20th*, 1958.

[20] Robertson and Whalley, *J.*, 1949, 848.

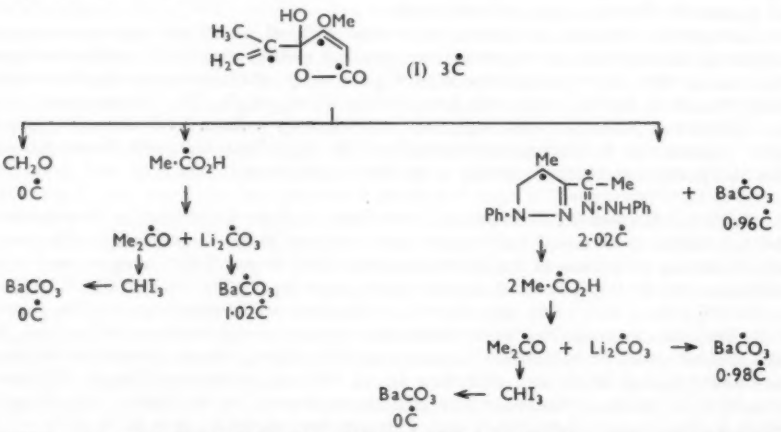
924. *Studies in Relation to Biosynthesis. Part XVIII.* Penicillic Acid.*

By A. J. Birch, G. E. Blance, and Herchel Smith.

The biosynthesis of penicillic acid (I) by *Penicillium cyclopium* Westling has been studied by feeding experiments with [2-^{14}C]mevalonic lactone and $CH_3 \cdot {}^{14}CO_2H$.

The classical mould metabolite penicillic "acid" has been shown [1,2] to possess the branched-chain lactone structure (I). Our interest in the biosynthesis arose from consideration of the possible ways for the production of the branched C_7 chain. If mevalonic acid [3] is involved as an intermediate, the biosynthesis would result either from the degradation of a C_{10} terpenoid chain or from the addition of the C_5 to a C_2 unit (probably acetic acid). In either case the process would be of considerable interest for the study of early stages in terpene biosynthesis. Other methods are potentially available for the production of branched carbon chains in Nature, notably those involving the introduction of C_1 units on to "methyl"-carbon atoms of straight chains derived by head-to-tail-linkage of acetic acid units. However, in penicillic acid the point of branching does not correspond to such an origin.

When *Penicillium cyclopium* Westling was grown on a Raulin–Thom medium containing [2-^{14}C]mevalonic lactone,[4] an insignificant amount (0·03%) of the radioactivity was incorporated into the penicillic acid and this radioactivity was found to be generally distributed along the carbon chain. The possibility of a biosynthetic relation between the terpenes and penicillic acid was thus discounted. Radioactivity from $CH_3 \cdot {}^{14}CO_2H$ was, however, incorporated to an appreciable extent (2·3%) and degradation of the labelled metabolite as illustrated in the scheme, showed this activity to be located to an equal extent upon carbon atoms 1, 3, and 5.



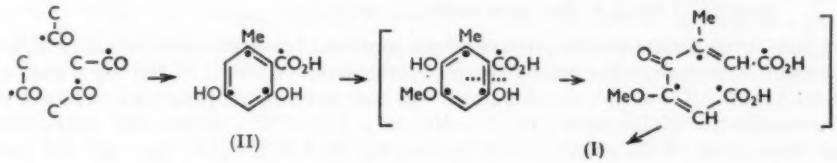
It will be seen that the distribution of radioactivity in the *iso*pentane portion parallels that encountered when $CH_3 \cdot {}^{14}CO_2H$ is biologically incorporated into terpenoid compounds. The above is therefore an important illustration of a route to a substance containing an "isoprene" unit which does not involve mevalonic acid. The exact route is not

* Part XVII, preceding paper.

[1] Birkinshaw, Oxford, and Raistrick, *Biochem. J.*, 1936, **30**, 394.
[2] Shaw, *J. Amer. Chem. Soc.*, 1946, **68**, 2510; Raphael, *J.*, 1947, 805.
[3] Wolf, Hoffman, Aldrich, Skeggs, Wright, and Folkers, *J. Amer. Chem. Soc.*, 1957, **79**, 1486.
[4] Cornforth, Cornforth, and Youhotsky-Gore, *Biochem. J.*, 1957, **66**, 10P.

XUM

clear: the possibility that it is akin to the biosynthesis of valine would require [5] all the radioactivity from $CH_3 \cdot {}^{14}CO_2H$ to be located on the carbon atom [1] of the *iso*valeric acid skeleton and is excluded by the " isoprenoid " labelling pattern. One possibility in accord with the above evidence is that the substance could be formed by oxidation and ring cleavage of a precursor related to orsellinic acid (II), possibly the 4-methyl ether, itself derived from a straight acetic-acid-based chain.* Recently Bassett and Tanenbaum [6] have presented



(II) (I)

indirect evidence of a similar cleavage of gentisic acid in the production of patulin by *P. patulum*, confirming a suggestion first made by Birkinshaw.[7] In this organism the gentisic acid appears to come from 6-methylsalicylic acid [7] which we have shown to arise by head-to-tail linkage of four acetic acid units.[8]

Experimental

General directions are as for Part XVII. Series (a) and (b) refer to materials derived from $CH_3 \cdot {}^{14}CO_2H$ and [2-^{14}C]mevalonic lactone respectively.

[^{14}C]*Penicillic Acid.*—*Penicillium cyclopium* Westling was cultured as previously described, except that on the seventh day $CH_3 \cdot {}^{14}CO_2Na$ (0·2 mc) or [2-^{14}C]mevalonic lactone (0·07 mc) was added. The cultures were harvested and the penicillic acid was isolated in the known manner. Additional purification could be effected by chromatography in light petroleum (b. p. 60—80°)–benzene on Florisil. The penicillic acid had m. p. 84° [Found: r.m.a., (a) $1{\cdot}07 \times 10^5$; (b) $4{\cdot}88 \times 10^3$].

Degradations of [^{14}C]*Penicillic Acid.*—Treatment of penicillic acid with phenylhydrazine in acetic acid as described earlier gave 3-acetyl-4 : 5-dihydro-4-methyl-1-phenylpyrazole phenylhydrazone, m. p. 175—176° (lit.,[1] m. p. 175—176°) [Found: r.m.a. (a) $7{\cdot}24 \times 10^4$ (2C, $7{\cdot}13 \times 10^4$)], and barium carbonate [Found: r.m.a., (a) $3{\cdot}45 \times 10^4$ (1C, $3{\cdot}57 \times 10^4$); (b) $5{\cdot}12 \times 10^2$]. Ozonolysis of penicillic acid in glacial acetic acid gave formaldehyde, examined as the dimedone derivative, m. p. 189° [Found: r.m.a. (a) 0; (b) $6{\cdot}72 \times 10^2$]. Kuhn–Roth oxidation of penicillic acid gave acetic acid (0·8 mol.), the lithium salt of which was pyrolysed,[9] giving $BaCO_3$(Me) [Found: r.m.a. (a) 0; (b) $5{\cdot}28 \times 10^2$], and $BaCO_3(CO_2H)$ [Found: r.m.a. (a) $3{\cdot}66 \times 10^4$ (1C, $3{\cdot}57 \times 10^4$); (b) $4{\cdot}93 \times 10^2$]. Kuhn–Roth oxidation of the phenylhydrazone gave acetic acid (1·6 mol.), the lithium salt of which was pyrolysed as before, to $BaCO_3$(Me) [Found: r.m.a. (a) $2{\cdot}36 \times 10^2$], and $BaCO_3(CO_2H)$ [Found: r.m.a. (a) $3{\cdot}49 \times 10^4$ (1C, $3{\cdot}57 \times 10^4$)].

We acknowledge the award of a Geigy Ltd. Scholarship (to G. E. B.) and are grateful to the Rockefeller Foundation (N.Y.) and the Distillers Co. Ltd. for financial assistance, and to Imperial Chemical Industries Limited for the loan of counting equipment. Cultures were grown by Miss M. Hay.

The University, Manchester, 13. [*Received, June 20th*, 1958.]

* Professor Ehrensvärd (Lund) has kindly informed us that he is engaged in tracer work to test this hypothesis independently considered by him.

[5] Strassman, Thomas, and Weinhouse, *J. Amer. Chem. Soc.*, 1955, **77**, 1261.
[6] Bassett and Tanenbaum, *Experientia*, 1958, **14**, 38.
[7] Birkinshaw, *Ann. Rev. Biochem.*, 1953, **22**, 379.
[8] Birch, Massy-Westropp, and Moye, *Austral. J. Chem.*, 1955, **8**, 539.
[9] Cornforth, Hunter, and Popjak, *Biochem. J.*, 1953, **54**, 597.

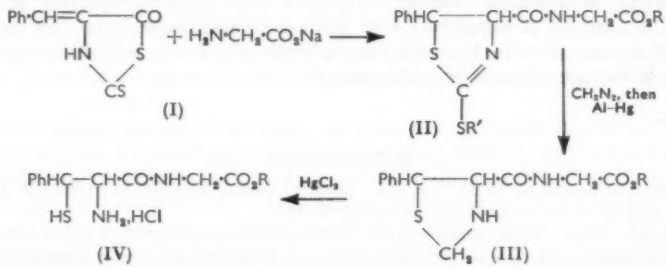
XUM

925. *Thiazolidines. Part I. Some Reactions of 4-Benzylidene-2-thiothiazolid-5-one with Glycine Derivatives.*

By D. O. Holland and P. Mamalis.

The higher-melting α-forms of 5-phenyl-2-thiothiazolidine-4-carbonylglycine (II; R = R′ = H) * and its derivatives undergo inversion in the presence of alkali to the lower-melting β-forms.

In a programme undertaken to prepare simple peptides of cysteine analogues the synthesis of β-phenylcysteinylglycine methyl ester hydrochloride (IV; R = Me) by Cook and Pollock's route [1] (I ⟶ IV) was examined. In contrast to their results we obtained two isomers of the thiazolidine ester (III; R = Me), m. p. 172—173° and 100—102° respectively, even when excess of the sodium salt of glycine was used in the first stage and the yields were very low. By treating the acid (II; R = R′ = H) * with alkali and methyl iodide



(which favour *S*-methylation [2]) instead of with dimethyl sulphate, we obtained 2-methylthio-5-phenylthiazoline-4-carbonylglycine (II; R = H, R′ = Me) crystalline rather than as an oil; esterification of this product with diazomethane also afforded a solid in contrast to the oil obtained by Cook and Pollock. Reduction of the resulting methylthiothiazoline ester with amalgamated aluminium gave 5-phenylthiazolidine-4-carbonylglycine methyl ester (III; R = Me), m. p. 104—105°, in 63% yield. This compound evidently corresponded to the β-form, m. p. 113—115°, described by Cook and Pollock. None of the α-form, m. p. 173°, was detected. It seems likely from these results that the low yields obtained in the original method arose, not only through the presence of α- and β-forms, but also because of the possibility of *N*-methylation in the reaction of the mercapto-acid (II; R = R′ = H) with diazomethane.

During the reaction of the sodium salt of glycine with 4-benzylidene-2-thiothiazolid-5-one (I) a considerable amount of hydrogen sulphide was evolved, indicating formation of the thiohydantoin (V; R = R′ = H), a reaction which Cook and Pollock considered took place only when a glycine ester was condensed with the thiazolidone. Isolation of the *S*-methylated thiohydantoin (V; R = H, R′ = Me) from the mother-liquors of the methylation of the acid (II; R = R′ = H) with methyl iodide and alkali, identical with the compound obtained by the direct *S*-methylation of the thiohydantoin (V; R = R′ = H), supported our view that the thiohydantoin was present as impurity in the original thiazolidine acid (II; R = R′ = H), m. p. 178—181°.

Hydrolysis of the β-form of the thiazolidine peptide ester (III; R = Me) with one equivalent of sodium hydroxide gave 5-phenylthiazolidinecarbonylglycine (III; R = H),

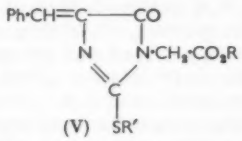
* The formulæ of thiothiazolidines [containing the –C(:S)–NH– grouping] are shown in this and the following four papers as mercaptothiazolines [containing the –C(SH)=N– grouping], so as to economise in structural formulæ, but the compounds are held to exist actually in the thiothiazolidine forms, at least in alcoholic solution (see p. 4591), and are named in the latter form.

[1] Cook and Pollock, *J.*, 1950, 1898.

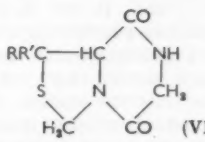
[2] Cf. Carrington and Waring, *J.*, 1950, 354.

m. p. *ca.* 80°, which when heated readily lost a molecule of water to give the dioxopiperazine (VI; R = H, R′ = Ph). Similar cyclisations have been reported [3] in the preparation of the dimethyl analogue (VI; R = R′ = Me). The dioxopiperazine was also obtained directly by heating the thiazolidine peptide ester (III; R = Me) with N-hydrochloric acid at 100°. Prolonged heating with 6N-hydrochloric acid gave 5-phenylthiazolidine-4-carboxylic acid hydrochloride.[4]

The reaction of glycine esters with 4-benzylidene-2-thiothiazolid-5-one has also been examined. Cook and Pollock,[1] using glycine ethyl ester, obtained a mixture of a thiothiazolidine ethyl ester (II; R = Et, R′ = H), m. p. 170°, and the crude thiohydantoin (V; R = Et, R′ = H), isolated as its *S*-methyl derivative. We, however, obtained,



(V)



(VI)

instead of the ester of m. p. 170°, a small quantity of an isomer, m. p. 230—231°, together with the pure thiohydantoin (V; R = Et, R′ = H). This ester on acid hydrolysis gave the isomeric acid (II; R = R′ = H), m. p. 224° (decomp.), but when alkali was used the acid (II; R = R′ = H) of m. p. 186—187° resulted, identical with that obtained from the sodium salt of glycine and 4-benzylidene-2-thiothiazolid-5-one. This compound also arose when the higher-melting acid was kept overnight in N-sodium hydroxide at room temperature.

Glycine methyl ester gave similar results. The higher-melting (m. p. 207—208°) 5-phenyl-2-thiothiazolidine-4-carbonylglycine methyl ester (II; R = Me, R′ = H) on alkaline hydrolysis gave the lower-melting thiazolidine acid (II; R = R′ = H) and on acid hydrolysis gave the isomer, m. p. 224° (decomp.). The ease of inversion of this form to the lower-melting isomer by mild treatment with alkali was further demonstrated when attempts were made to prepare its *S*-methyl derivative (II; R = H, R′ = Me) by reaction with methyl iodide and alkali; the product was identical with that derived from the isomer of m. p. 186—187°.

When 4-benzylidene-2-thiothiazolid-5-one was allowed to react with glycine ethyl ester hydrochloride in the presence of one equivalent of 2-aminopyridine [5] much hydrogen sulphide was evolved, the sole product isolated being the thiohydantoin (V; R = Et, R′ = H).

The results described here indicate that under weakly basic conditions the higher-melting peptide (II) can be formed, although the major products are thiohydantoins, while under more strongly alkaline conditions the lower-melting isomer is produced. Evidence to support this arises from the ease with which inversion to the lower-melting acid or its derivatives takes place in the presence of alkali. The latter compounds evidently correspond to the β-form of the ester (III; R = Me) described by Cook and Pollock, and the higher-melting isomers are related to the α-form.

Experimental

2-Methylthio-5-phenylthiazoline-4-carbonylglycine (*β-Form*).—A mixture of 5-phenyl-2-thiothiazolidine-4-carbonylglycine, m. p. 178—181° (20 g.) (prepared from 4-benzylidene-2-thiothiazolid-5-one and excess of the sodium salt of glycine essentially as described by Cook and Pollock [1]), and methyl iodide (8·5 ml.) in N-sodium hydroxide (135 ml.) was stirred for 1 hr. Next day it was acidified with hydrochloric acid, and the precipitated gum extracted with chloroform. The dried extract was concentrated to small volume and treated with light

[3] Neher, Spillmann, Werner, Wettstein, and Miescher, *Helv. Chim. Acta*, 1946, **29**, 1874; Süs, *Annalen*, 1948, **561**, 31; Süs and Rosenberger, *ibid.*, 1949, **564**, 54.
[4] Kashida and Yamanaka, *J. Pharm. Soc. Japan*, 1953, **73**, 953 (*Chem. Abs.*, 1954, **48**, 11,394).
[5] Cook, Hunter, and Pollock, *J.*, 1950, 1892.

petroleum (b. p. 80—100°), β-2-*methylthio*-5-*phenylthiazoline*-4-*carbonylglycine* (12·25 g.), m. p. 130—132°, slowly separating as needles. Recrystallised from aqueous methanol, this had m. p. 131—133° (Found: C, 50·3; H, 4·6; N, 9·0; S, 19·8. $C_{13}H_{14}O_3N_2S_2$ requires C, 50·3; H, 4·6; N, 9·0; S, 20·6%).

4-*Benzylidene*-4 : 5-*dihydro*-2-*methylthio*-5-*oxoglyoxalin*-1-*ylacetic acid* separated in small amount on further concentration of the mother-liquors from the above preparation. It recrystallised from chloroform–methanol as needles, m. p. 203—205° (Found: C, 56·7; H, 4·5; N, 10·1. $C_{13}H_{12}O_3N_2S$ requires C, 56·6; H, 4·4; N, 10·1%).

2-*Methylthio*-5-*phenylthiazoline*-4-*carbonylglycine Methyl Ester* (β-*Form*).—This *ester* was obtained in 82% yield on esterifying a suspension of the acid (9 g.) in ether (50 ml.) with diazomethane in the usual way. It recrystallised from ether–light petroleum as needles, m. p. 80—81° (Found: C, 52·1; H, 5·0; N, 9·1. $C_{14}H_{16}O_3N_2S_2$ requires C, 51·9; H, 5·0; N, 8·7%).

5-*Phenylthiazolidine*-4-*carbonylglycine Methyl Ester* (β-*Form*).—A solution of 2-methylthio-5-phenylthiazoline-4-carbonylglycine methyl ester (3·5 g.) in methanol (70 ml.) was added to amalganated aluminium foil (2 g.). Next day methanol (70 ml.) was added, and the mixture boiled and filtered and the residue extracted with hot methanol (2 × 50 ml.). When the combined filtrate and extracts were concentrated to small volume the required product separated. Ether (20 ml.) was then added and the solid, m. p. 104—105° (1·9 g., 63%), removed. It recrystallised from aqueous alcohol with unchanged m. p. (Found: C, 55·6; H, 5·9; N, 9·9. Calc. for $C_{13}H_{16}O_3N_2S$: C, 55·8; H, 5·7; N, 10·0%).

This compound was obtained in 60% overall yield from 2-methylthio-5-phenylthiazoline-4-carbonylglycine by omitting the purification of the intermediate ester.

5-*Phenylthiazolidine*-4-*carbonylglycine* (β-*Form*).—The methyl ester (0·5 g.) was kept in N-sodium hydroxide (2 ml.) and 2 : 1 v/v aqueous alcohol (6 ml.) for 1 hr. at room temperature. The resulting clear solution was extracted with ether, the aqueous layer acidified to pH 4, and the product extracted with chloroform (4 × 50 ml.). The residual *acid* from the dried chloroform extract, recrystallised from ethyl acetate, had m. p. *ca.* 80° (decomp.). It was soluble in sodium hydrogen carbonate solution (Found: C, 53·9; H, 5·6; N, 10·5. $C_{12}H_{14}O_3N_2S$ requires C, 54·2; H, 5·3; N, 10·5%).

The *dioxopiperazine* (VIII; R = H, R′ = Ph) was obtained by heating this acid for 5 min. at 120—130°. The acid melted with decomposition and then resolidified. The solid recrystallised from alcohol as plates, m. p. 203—204° (Found: C, 58·1; H, 4·9; N, 10·9. $C_{12}H_{12}O_2N_2S$ requires C, 58·1; H, 4·8; N, 11·3%).

5-*Phenylthiazolidine*-4-*carboxylic Acid* (β-*Form*).—5-Phenylthiazolidine-4-carbonylglycine methyl ester (0·5 g.) was heated under reflux in 6N-hydrochloric acid (5 ml.) for 6 hr. and the resulting solution concentrated to small volume. β-5-Phenylthiazolidine-4-carboxylic acid hydrochloride (0·35 g.), m. p. 192—193°, separated. It recrystallised from alcohol–ether with unchanged m. p. [lit.,[4] m. p. 193° (decomp.)] (Found: C, 49·0; H, 5·5; Cl, 14·6. Calc. for $C_{10}H_{12}O_2NSCl$: C, 49·0; H, 4·9; Cl, 14·5%). When a solution of the hydrochloride in water was neutralised with N-sodium hydroxide β-5-phenylthiazolidine-4-carboxylic acid separated. Recrystallised from water, it had m. p. 214° (decomp.) [lit.,[4] m. p. 213° (decomp.)] (Found: N, 7·1. Calc. for $C_{10}H_{11}O_2NS$: N, 6·7%).

Reaction between 4-*Benzylidene*-2-*thiothiazolid*-5-*one and Glycine Ethyl Ester.*—(*a*) The thiazolidone (8·8 g.), glycine ethyl ester hydrochloride (6·0 g.), and N-sodium hydroxide (40 ml.) were heated under reflux in ethanol (80 ml.) for 2 hr. The resulting solution was kept at room temperature overnight and the white solid that separated was removed (0·98 g.; m. p. 220—222°). Recrystallisation from ethanol gave the α-*form* of 5-*phenyl*-2-*thiothiazolidine*-4-*carbonylglycine ethyl ester* as needles, m. p. 230—231° (Found: C, 51·8; H, 5·3; N, 9·0. $C_{14}H_{16}O_3N_2S_2$ requires C, 51·9; H, 5·0; N, 8·7%). The filtrate, on concentration, yielded ethyl 4-benzylidene-4 : 5-dihydro-2-mercapto-5-oxoglyoxalin-1-ylacetate as yellow platelets (5·4 g.), m. p. 158—160°, raised to m. p. 167—170° (lit., 160°) by recrystallisation from ethanol (Found: C, 57·6; H, 4·7; N, 9·8. Calc. for $C_{14}H_{14}O_3N_2S$: C, 57·9; H, 4·9; N, 9·7%). On reaction with dimethyl sulphate and sodium hydroxide, as described by Cook and Pollock, this compound gave the *S*-methyl derivative, m. p. 122° (Found: C, 59·3; H, 5·3; N, 8·9. Calc. for $C_{15}H_{16}O_3N_2S$: C, 59·3; H, 5·3; N, 9·2%).

(*b*) When the reaction between the thiazolidone (4·4 g.) and glycine ethyl ester hydrochloride (3 g.) in methanol (50 ml.) was effected in the presence of 2-aminopyridine (4·2 g.) under reflux for 5 hr. there was considerable evolution of hydrogen sulphide and when the solution

XUM

was cooled ethyl 4-benzylidene-4 : 5-dihydro-2-mercapto-5-oxoglyoxalin-1-ylacetate (1·4 g.) separated; it formed yellow needles (from methanol), m. p. and mixed m. p. 165—168° (Found: C, 57·5; H, 4·9; N, 10·1%).

Reaction between 4-Benzylidene-2-thiothiazolid-5-one and Glycine Methyl Ester.—The thiazolidone (2·2 g.) and glycine methyl ester hydrochloride (1·4 g.) were heated under reflux in N-sodium hydroxide (10 ml.) for 2 hr., then cooled to room temperature and kept overnight. The *α-form of 5p-henyl-2-thiothiazolidine-4-carbonylglycine methyl ester* (0·7 g.) separated as needles, m. p. 200—202°, raised to 207—208° by recrystallisation from methyl alcohol (Found: C, 50·6; H, 4·8; N, 8·8. $C_{13}H_{14}O_3N_2S_2$ requires C, 50·4; H, 4·6; N, 9·0%). From the concentrated filtrate *methyl 4-benzylidene-4 : 5-dihydro-2-mercapto-5-oxoglyoxalin-1-ylacetate* (0·45 g.) separated as yellow prisms, m. p. 160—161° (from methanol) (Found: C, 56·3; H, 4·7; N, 10·1. $C_{13}H_{12}O_3N_2S$ requires C, 56·6; H, 4·4; N, 10·1%).

4-Benzylidene-4 : 5-dihydro-2-mercapto-5-oxoglyoxalin-1-ylacetic Acid.—Ethyl 4-benzylidene-4 : 5-dihydro-2-mercapto-5-oxoglyoxalin-1-ylacetate (1 g.) in N-sodium hydroxide (12 ml.) was heated on a steam-bath for 20 min. The resulting red solution was filtered from a little insoluble material and acidified with hydrochloric acid; *4-benzylidene-4 : 5-dihydro-2-mercapto-5-oxoglyoxalin-1-ylacetic acid* (0·7 g.) which separated recrystallised from ethanol as yellow needles, m. p. 257° after softening from 252° (Found: C, 55·1; H, 3·7; N, 10·8. $C_{12}H_{10}O_3N_2S$ requires C, 55·1; H, 3·9; N, 10·7%). Hydrolysis of the methyl ester in the same way also yielded the 2-mercapto-acid, m. p. and mixed m. p. 240—242° (Found: C, 55·0; H, 3·9; N, 11·1%).

Treatment of a solution of the mercapto-acid (0·6 g.) in N-sodium hydroxide (5 ml.) with methyl iodide yielded, after acidification of the mixture with acetic acid, the 2-methylthio-derivative, m. p. 208—209°, not depressed when mixed with the product described above arising from *S*-methylation of crude (m. p. 178—181°) 5-phenyl-2-thiothiazolidine-4-carbonylglycine.

Hydrolysis of α-5-Phenyl-2-thiothiazolidine-4-carbonylglycine Ethyl Ester.—(a) *With acid.* The ester (1·0 g.) was heated under reflux for 1 hr. in concentrated hydrochloric acid (4 ml.), water (20 ml.), and dioxan (10 ml.). When the resulting solution was cooled and diluted with water the *α-form of 5-phenyl-2-thiothiazolidine-4-carbonylglycine* separated as needles, m. p. 223—224° (0·7 g.), not raised on recrystallisation from aqueous alcohol (Found: C, 49·1; H, 4·1; N, 9·1. $C_{12}H_{12}O_3N_2S_2$ requires C, 48·7; H, 4·1; N, 9·4%).

(b) *With alkali.* The ester (0·4 g.) in N-sodium hydroxide (5 ml.) was kept overnight and the resulting solution acidified with N-hydrochloric acid. An oil separated which solidified on warming (m. p. 183—184°). Recrystallisation from aqueous alcohol gave needles of the β-form of 5-phenyl-2-thiothiazolidine-4-carbonylglycine, m. p. 186—187°, not depressed on admixture with the crude acid of m. p. 178—181° obtained by Cook and Pollock's method (Found: C, 48·2; H, 4·1; N, 9·5; S, 21·6%). Each gave an *S-benzylthiuronium salt*, m. p. 185—186° (decomp.) not depressed when mixed (the m. p. depends on the rate of heating) (Found: C, 52·0; H, 4·9; N, 12·2; S, 20·4. $C_{20}H_{22}O_3N_4S_3$ requires C, 52·0; H, 4·8; N, 12·1; S, 20·8%).

Inversion of α-5-Phenyl-2-thiothiazolidine-4-carbonylglycine into the β-Form.—The α-acid (0·05 g.) was kept overnight in N-sodium hydroxide (1 ml.), and the solution acidified. The β-acid which separated, on crystallisation from water, formed needles (0·03 g.), m. p. and mixed m. p. 183—185°.

S-Methylation of α-5-Phenyl-2-thiothiazolidine-4-carbonylglycine.—A solution of the α-acid (0·25 g.) in N-sodium hydroxide (2 ml.) was treated with methyl iodide (0·1 ml.). The mixture was kept overnight and, after acidification with dilute hydrochloric acid, extracted with chloroform. After being washed and dried, the extract was concentrated to small volume and diluted with light petroleum; the β-form of 2-methylthio-5-phenylthiazoline-4-carbonylglycine (0·1 g.) slowly separated. After recrystallisation from aqueous methanol it had m. p. and mixed m. p. 129—131°.

BEECHAM RESEARCH LABORATORIES LTD.,
BROCKHAM PARK, BETCHWORTH, SURREY.

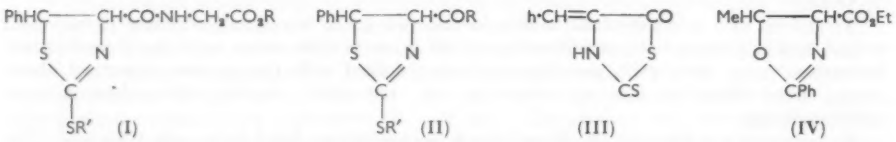
[*Received, July 7th,* 1958.]

926. *Thiazolidines. Part II.*[1] *Some Reactions of 5-Phenyl-2-thiothiazolidine-4-carboxylic Acid.*

By D. O. Holland and P. Mamalis.

Like the α-form of 5-phenyl-2-thiothiazolidine-4-carbonylglycine (I; R = R′ = H),* *cis*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (II; R = OH, R′ = H) and its derivatives have been inverted to the lower-melting *trans*-isomers by the action of alkali. The inference that the α-peptide has the *cis*- and the β-peptide the *trans*-configuration has been confirmed by synthesis of the latter from the *trans*-acid (II; R = OH, R′ = H) by way of the hydrazide (II; R = NH·NH$_2$, R′ = H). Attempts to use this route to the *cis*-peptide were unsuccessful.

It has been shown [1] that the higher-melting or α-isomer of 5-phenyl-2-thiothiazolidine-4-carbonylglycine (I; R = R′ = H) * can be converted into the lower-melting β-isomer by the action of alkali. It was of interest to correlate these by attempting their synthesis from the two isomeric 5-phenyl-2-thiothiazolidine-4-carboxylic acids (II; R = OH, R′ = H) of Chatterjee, Cook, Heilbron, and Levy.[2]



The lower-melting (m. p. 175—176°) 5-phenyl-2-thiothiazolidine-4-carboxylic acid (II; R = OH, R′ = H) which Chatterjee *et al.*[2] designated the α-form has been shown by Sicher *et al.*[3] probably to possess the *trans*-configuration. It was readily obtained by the action of methanolic potassium hydroxide on 4-benzylidene-2-thiothiazolid-5-one [2] (III). Preparation of the *cis*-form, m. p. 235° (decomp.), from the same starting material by reaction with aqueous sodium carbonate [2] gave low and variable yields in our hands: at best 20% was produced, together with 50% of the *trans*-isomer, by heating the reactants on the steam-bath for 30—45 min. Longer heating gave a greater proportion of the *trans*-acid and after six hours only this form could be isolated. The inference that the higher-melting *cis*-form could be converted into the lower-melting *trans*-form was confirmed by heating a sample of the former in aqueous sodium carbonate or sodium hydroxide for several hours, complete conversion occurring. It seems likely from this that the higher-melting α-form and the lower-melting β-form of the peptide (I; R = R′ = H) and their derivatives possessed the *cis*- and the *trans*-configuration respectively and this was confirmed by the synthesis, described below, of the β-form of (I; R = R′ = H) from *trans*-5-phenyl-2-thiothiazolidine-4-carboxylic acid.

The *cis*- and the *trans*-methyl and -ethyl esters (II; R = OMe or OEt, R′ = H) on hydrolysis behaved similarly to the α- and β-peptide esters (I; R = Me or Et, R′ = H), giving the respective acids when acid was used but only the *trans*-acid with cold alkali. Attempts to hydrolyse the *trans*-methyl ester (II; R = OMe, R′ = H) with aqueous-ethanolic hydrochloric acid gave the ethyl ester, and the *trans*-acid could be esterified by heating it with methanol in the absence of catalyst.

Hydrolysis of the two isomeric 5-phenyl-2-thiothiazolidine-4-carboxyamides (II; R = NH$_2$, R′ = H), prepared by the action of one equivalent of cold aqueous ammonia on 4-benzylidene-2-thiothiazolid-5-one (III), as described by Chatterjee *et al.*,[2] fitted the same

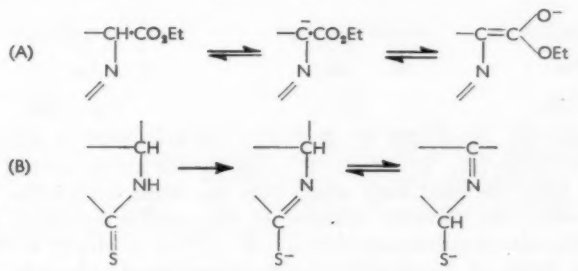
* See footnote on p. 4584.

[1] Part I, preceding paper.
[2] Chatterjee, Cook, Heilbron, and Levy, *J.*, 1948, 1337.

pattern. The higher-melting isomer, m. p. 241—242° (decomp.), on acid hydrolysis afforded a convenient synthesis of *cis*-5-phenyl-2-thiothiazolidine-4-carboxylic acid, while the other isomer, m. p. 180—181°, gave the *trans*-acid. Both gave the *trans*-acid on treatment with cold N-sodium hydroxide. *cis*-5-Phenyl-2-thiothiazolidine-4-carboxylic acid itself was unaffected by cold alkali.

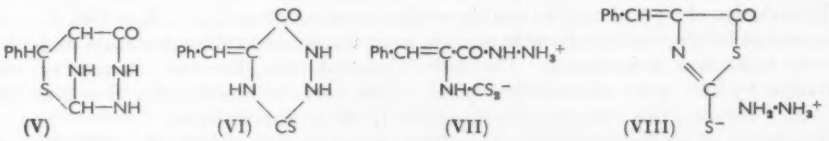
The action of aqueous ammonia on the *trans*-methyl ester (II; R = OMe, R′ = H) gave the *trans*-amide (II; R = NH_2, R′ = H), but from the *cis*-methyl ester a mixture was obtained from which only the *trans*-amide could be isolated pure.

In the analogous alkaline hydrolysis of the two forms of 5-methyl-2-phenyl-Δ^2-oxazoline ethyl ester (IV), Elliott [4] postulated that inversion is effected at the 4-carbon atom, by enolisation of the ethoxycarbonyl group before hydrolysis (scheme A).



That inversion in the thiothiazolidines also took place at position 4 and not by opening of the ring between the sulphur atom and $C_{(5)}$ can be inferred from the fact that rearrangement of the thiazolidone (III) with either sodium carbonate or ammonia gave some of the *cis*-derivatives in the first place. The inversion therefore probably follows Elliott's mechanism. However, since the free *cis*-acid (II; R = OH, R′ = H) can be inverted with alkali, it is possible that inversion at $C_{(4)}$ can occur as shown in scheme B.

For the attempted synthesis of the two 5-phenyl-2-thiothiazolidine-4-carbonylglycines (I; R = R′ = H) from the corresponding 5-phenyl-2-thiothiazolidinecarboxylic acids the azide method was used. The action of excess of hydrazine hydrate on the *trans*-methyl ester (II; R = OMe, R′ = H) gave a yellow product $C_{10}H_9ON_3S_3$, m. p. 265° (decomp.), insoluble in dilute acid but soluble in alkali, instead of the expected hydrazide (II; R = NH·NH_2, R′ = H). Two structures (V) and (VI) were considered for this compound, the first arising by ring-closure of the hydrazide (II; R = NH·NH_2, R′ = H), and the second by rupture of the 1 : 5-bond and ring turning. Compound (VI) has been reported



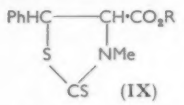
by Cook, Hunter, and Pollock [5] to be formed by the action of hydrazine hydrate on 4-benzylidene-2-thiothiazolid-5-one. We obtained, however, an unstable solid, probably the internal dithiocarbamic salt (VII) rather than the isomeric hydrazine salt (VIII) since it was colourless. This, when heated with water, lost hydrogen sulphide to yield the suspected triazine (VI) identical with the compound obtained from the ester (II; R = OMe, R′ = H) and hydrazine hydrate. Both gave the same methyl derivative, m. p. 163—164°,

[3] Sicher, Svoboda, and Farkas, *Coll. Czech. Chem. Comm.*, 1955, **20**, 1439.
[4] Elliott, *J.*, 1949, 589.
[5] Cook, Hunter, and Pollock, *J.*, 1950, 1892.

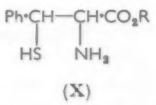
on reaction with methyl iodide and sodium hydroxide. The methyl derivative, m. p. 227° (decomp.), described by Cook *et al.*[5] was not obtained.

The required hydrazide (II; R = NH·NH_2, R′ = H) was eventually obtained with the triazine (VI) by slow addition of one equivalent of hydrazine hydrate to a methanolic solution of the methyl ester (II; R = OMe, R′ = H). It formed a crystalline hydrochloride and benzylidene derivative. None of the compound of m. p. 265° (decomp.) was produced when the hydrazide was heated with an excess of hydrazine hydrate, thus rendering the structure (V) unlikely.

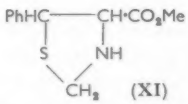
The hydrazide on reaction with nitrous acid and then glycine ethyl ester gave an oily peptide ester which on hydrolysis with dilute acid or alkali gave β-5-phenyl-2-thiothiazolidine-4-carbonylglycine (I; R = R′ = H). It is evident that this peptide possesses the *trans*-configuration.



(IX)



(X)



(XI)

Attempts to prepare the *cis*-peptide (I; R = R′ = H) from methyl *cis*-5-phenyl-2-thiothiazolidine-4-carboxylate (II; R = OMe, R′ = H) by the above method were unsuccessful, a mixture being obtained from which only the suspected triazine (VI) was obtained pure. Attention was therefore directed to the possible synthesis of the 2-methylthio-5-phenylthiazoline-4-carbonylglycines (I; R = H, R′ = Me) by a similar procedure from the two forms of 2-methylthio-5-phenylthiazoline-4-carboxylic acid (II; R = OH, R′ = Me).

trans-5-Phenyl-2-thiothiazolidine-4-carboxylic acid (II; R = OH, R′ = H) with dimethyl sulphate and N-sodium hydroxide yielded an oil, possibly a mixture of the 3-methyl derivative (IX; R = H) with the required 2-methylthio-acid (cf. Carrington and Waring [6]). By the use of methyl iodide and two equivalents of N-sodium hydroxide, however, the methylthio-acid (II; R = OH, R′ = Me) was obtained crystalline. Kashida and Yamanaka [7] obtained a 66% yield of what was probably the same acid by methylation with diazomethane followed by alkaline hydrolysis of the crude methyl ester. Esterification of *trans*-2-methylthio-5-phenylthiazoline-4-carboxylic acid with diazomethane gave the ester (II; R = OMe, R′ = Me) as an oil, which on reaction with hydrazine hydrate in methanol gave a good yield of the hydrazide (II; R = NH·NH_2, R′ = Me). From this by conversion into the azide (not isolated) and reaction with glycine methyl ester the *trans*-form of 2-methylthio-5-phenylthiazoline-4-carbonylglycine methyl ester (I; R = R′ = Me) was formed, identical with the product obtained by the esterification of the β-*S*-methylated acid (I; R = H, R′ = Me) with diazomethane.[1]

Methylation of *cis*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (II; R = OH, R′ = H) with methyl iodide and N-sodium hydroxide gave the corresponding *S*-methyl derivative with no indication of inversion. The derived methyl ester, however, on reaction with hydrazine hydrate gave an excellent yield of the *trans*-hydrazide (II; R = NH·NH_2, R′ = Me), showing this route to the *cis*-peptide (I) to be impracticable.

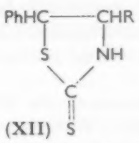
Treatment of *cis*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (II; R = OH, R′ = H) with an excess of diazomethane gave a mixture of two methylated methyl esters, one of which was identical with the *cis*-form of methyl 2-methylthio-5-phenylthiazoline-4-carboxylate (II; R = OMe, R′ = Me). The other, which was not identical with the *trans*-isomer thereof, was probably the *N*-methyl isomer (IX; R = Me), a conclusion supported by ultraviolet absorption measurements.

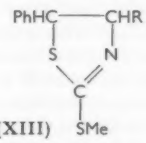
From methyl *trans*-2-methylthio-5-phenylthiazoline-4-carboxylate (II; R = OMe, R′ = Me) *threo*-phenylcysteine [3] (X; R = H) was synthesized by the method used by

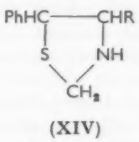
[6] Carrington and Waring, *J.*, 1950, 354.
[7] Kashida and Yamanaka, *J. Pharm. Soc. Japan*, 1953, **73**, 953 (*Chem. Abs.*, 1954, **48**, 11394).

Cook, Hunter, and Pollock [5] for the preparation of phenylcysteine amide. Reduction of the methyl ester (II; R = OMe, R′ = Me) with amalgamated aluminium gave methyl 5-phenylthiazolidine-4-carboxylate (XI). Ring opening of the thiazolidine ester with mercuric chloride in aqueous methanol and decomposition of the resulting mercaptide with hydrogen sulphide gave a good yield of the hydrochloride of phenylcysteine methyl ester (X; R = Me) from which on hydrolysis with hydrochloric acid the amino-acid hydrochloride, m. p. 204° (decomp.), was obtained.

Examination of the ultraviolet absorption spectra of many of the compounds described in this and the preceding paper has shown that to a large extent the 2-thiothiazolidine derivatives exist in alcoholic solution in the form (XII). They exhibit almost identical


(XII)


(XIII)


(XIV)

absorption with a characteristic maximum at about 281 mμ, whereas stabilisation of the thiazoline structure by *S*-methylation (XIII) leads to the disappearance of the peak. Variation of the group R or stereochemical configuration appears to have little or no influence on the absorption. The absorption also disappears when the C=S group in the thiazolidines is replaced by methylene (XIV).

Experimental

cis-5-*Phenyl*-2-*thiothiazolidine*-4-*carboxylic Acid*.—To a hot solution of sodium carbonate (75 g.) in water (600 ml.) 4-benzylidene-2-thiothiazolid-5-one [2] (30 g.) was added with stirring and the mixture was heated on a steam-bath for 45 min. The hot solution was filtered from a little insoluble material and carefully acidified with hydrochloric acid. The solid that separated was removed, washed with water, and dried. Recrystallising the solid from methanol gave the *cis*-acid (7·9 g.) as needles, m. p. 230—234° (decomp.), raised to 235° (decomp.) on recrystallisation from aqueous methanol (Found: C, 50·0; H, 3·8; N, 5·8. Calc. for $C_{10}H_9O_2NS_2$: C, 50·2; H, 3·8; N, 5·9%). From the methanolic filtrate on dilution with much water about 20 g. of solid were deposited. This was removed and treated with a solution of sodium hydrogen carbonate. The insoluble residue (5·1 g.), m. p. 100—101°, on recrystallisation from chloroform–light petroleum was obtained as needles, m. p. 105—106°, undepressed on admixture with methyl *trans*-5-phenyl-2-thiothiazolidine-4-carboxylate described below. This compound was apparently formed by esterification of the *trans*-acid during the crystallisation of the *cis*-acid from methanol. From the sodium hydrogen carbonate extract the *trans*-acid (14·8 g.) was obtained on acidification.

Inversion of cis- *to* trans-5-*Phenyl*-2-*thiothiazolidine*-4-*carboxylic Acid*.—The *cis*-acid (0·5 g.) was heated on a steam-bath for 5 hr. in a solution of sodium carbonate (2 g.) in water (40 ml.). The mixture was then cooled and acidified, the *trans*-acid (0·36 g.) separating. On recrystallisation from aqueous acetic acid it was obtained as needles, m. p. and mixed m. p. 175—176°.

Methyl trans-5-*Phenyl*-2-*thiothiazolidine*-4-*carboxylate*.—The *trans*-acid (0·5 g.) in methanol (5 ml.) was saturated with hydrogen chloride, and the mixture kept at 0° overnight. The solution was then concentrated to small volume and diluted with water, the *methyl ester* separating as colourless leaflets (0·37 g.), m. p. 105—106°, not raised when recrystallised from aqueous methanol (Found: C, 52·2; H, 4·6; N, 5·6. $C_{11}H_{11}O_2NS$ requires C, 52·2; H, 4·4; N, 5·5%). The same compound was obtained when concentrated sulphuric acid (3 drops) was used instead of hydrogen chloride. The methyl ester also arose when the *trans*-acid (2·0 g.) was refluxed in methanol (20 ml.) for 0·5 hr. After evaporation of the solution to dryness, the residue was extracted with a solution of sodium hydrogen carbonate to leave the ester (0·8 g.), m. p. and mixed m. p. 101—102°.

The methyl ester also arose on transesterification from the ethyl ester (1·0 g.) in methyl alcohol (15 ml.) overnight in the presence of a trace of sodium methoxide. The resulting solution was neutralised with dilute hydrochloric acid and concentrated to about 5 ml., the

methyl ester (0·55 g.) separating. Its m. p. (104—105° after recrystallisation from aqueous methanol) was not depressed on admixture with a pure specimen, but depressed on admixture with the ethyl ester.

Ethyl trans-5-*Phenyl*-2-*thiothiazolidine*-4-*carboxylate*.—Esterification of the *trans*-acid (1·0 g. in ethanol (15 ml.) as above gave the *ethyl ester* as leaflets (1·05 g.). It was obtained as needles, m. p. 112·5°, after shrinking from 99°, on recrystallisation from aqueous ethanol (Found: C, 53·5; H, 5·0; N, 4·9. $C_{12}H_{13}O_2NS_2$ requires C, 54·0; H, 4·9; N, 5·2%). The ethyl ester was also obtained by heating the methyl ester (1·0 g.) in ethanol (20 ml.) for 1 hr. on a steam-bath in the presence of dissolved sodium (*ca.* 0·05 g.). When the solution was concentrated and acidified with dilute hydrochloric acid leaflets (0·6 g.) separated, m. p. 105—107°, undepressed on admixture with the ethyl ester, but markedly depressed on admixture with the starting material. Transesterification also took place when the *trans*-methyl ester (1 g.) in ethanol (10 ml.) was heated under reflux for 0·5 hr. with concentrated hydrochloric acid (2 ml.). When the cooled solution was diluted with water the ethyl ester (0·6 g.) separated as needles, m. p. and mixed m. p. 109—110° after shrinking at 99°.

Methyl cis-5-*Phenyl*-2-*thiothiazolidine*-4-*carboxylate*.—A suspension of the *cis*-acid (0·6 g.) in methanol (7 ml.) was saturated with hydrogen chloride and kept at room temperature overnight. The white solid *ester* (0·35 g.) that had separated was removed and recrystallised from aqueous methanol as plates, m. p. 163—164° (Found: C, 52·2; H, 4·5; N, 5·8. $C_{11}H_{11}O_2NS_2$ requires C, 52·3; H, 4·4; N, 5·5%).

Ethyl cis-5-*Phenyl*-2-*thiothiazolidine*-4-*carboxylate*.—Esterification of the *cis*-acid (5 g.) with ethanol and hydrogen chloride as described above gave the required *ethyl ester* (4·35 g.) as long needles, m. p. 154—155° (from alcohol) (Found: C, 53·7; H, 5·0; N, 5·1%).

Hydrolysis of Esters of cis-5-*Phenyl*-2-*thiothiazolidine*-4-*carboxylic Acid*.—(a) *With acid*. The methyl ester (1·0 g.) was hydrolysed under reflux in dioxan (10 ml.) and water (20 ml.) with concentrated hydrochloric acid (4 ml.) for 1·5 hr. On cooling of the mixture a solid separated which was removed and dissolved in aqueous sodium hydrogen carbonate. The resulting solution was filtered from a little insoluble residue and acidified with dilute hydrochloric acid; the *cis*-acid (0·8 g.) which separated had m. p. 229° (decomp.), not depressed on admixture with a pure specimen. From the ethyl ester (0·5 g.) there was likewise obtained 0·38 g. of the *cis*-acid.

(b) *With alkali*. A mixture of the methyl ester (0·5 g.) in N-sodium hydroxide (3 ml.) was heated on a steam-bath for 10 min., then kept at room temperature for 3 hr. The resulting solution was filtered and acidified with dilute hydrochloric acid, an oil separating, which solidified when warmed and scratched (0·42 g., m. p. 169—171°). When this recrystallised from aqueous ethanol there separated first a small quantity (0·05 g.) of the *cis*-acid, m. p. 229—230° (decomp.) (from aqueous alcohol), followed by the *trans*-acid (0·35 g.), m. p. 172—173°, raised to 175—176° on recrystallisation from aqueous ethanol and not depressed on admixture with an authentic specimen.

Hydrolysis of Esters of trans-5-*Phenyl*-2-*thiothiazolidine*-4-*carboxylic Acid*.—(a) *With acid*. When the *trans*-methyl ester (1 g.) was hydrolysed under reflux in dilute hydrochloric acid (25 ml.) for 1·5 hr., the *trans*-acid was obtained as plates (0·75 g.), m. p. and mixed m. p. 176—177°. Similarly from the ethyl ester (0·5 g.) the *trans*-acid (0·45 g.) was obtained.

(b) *With alkali*. A mixture of the *trans*-methyl ester (0·2 g.) and N-sodium hydroxide (1 ml.) was heated until a clear solution was obtained, and then kept overnight at room temperature. On acidification of the solution with dilute hydrochloric acid, the *trans*-acid (0·15 g.) was precipitated (m. p. 174—176°).

cis- *and* trans-5-*Phenyl*-2-*thiothiazolidine*-4-*carboxyamide*.—To a suspension of 4-benzylidene-2-thiothiazolid-5-one (12 g.) in water (80 ml.), ammonia (*d* 0·88; 20 ml.) was added to give a red solution which soon became yellow. Next day the *cis*-amide (4·3 g.), m. p. 230—232° (decomp.), that had separated was removed. On recrystallisation from methanol it was obtained as leaflets, m. p. 240° (decomp.) [this corresponds to the β-amide, m. p. 229—230° (decomp.), of Chatterjee *et al.*[2]] (Found: C, 50·4; H, 4·5; N, 11·8. Calc. for $C_{10}H_{10}ON_2S_2$: C, 50·5; H, 4·3; N, 11·8%). Acidification of the ammoniacal filtrate with concentrated hydrochloric acid precipitated the *trans*-amide (7·5 g.), m. p. 170—172°, obtained as pale yellow needles, m. p. 180—181°, from methanol (corresponding to the α-form, m. p. 178°, of Chatterjee *et al.*[2]) (Found: C, 50·5; H, 4·5; N, 11·9%).

When methyl *cis*-5-phenyl-2-thiothiazolidine-4-carboxylate (0·25 g.) was kept in ammonia

(*d* 0·88; 2 ml.) for 15 hr. and the resulting solution was diluted with water (10 ml.) and neutralised with hydrochloric acid the *trans*-amide (0·15 g.) separated; it had m. p. 172—173°, raised to 181—182° on recrystallisation from aqueous methanol. The same amide (0·19 g.) also arose from the *trans*-methyl ester (0·20 g.). Both samples failed to depress the m. p. of the lower-melting amide described above.

Hydrolysis of cis-*5-Phenyl-2-thiothiazolidine-4-carboxyamide.*—(a) *With acid.* The amide (0·5 g.) was heated under reflux for 15 hr. in a mixture of dioxan (4 ml.), water (3 ml.), and concentrated hydrochloric acid (4 ml.). The solid that separated from the cooled solution was removed and extracted with sodium hydrogen carbonate solution, and the extract was clarified with charcoal. On acidification the extract yielded the *cis*-acid (0·25 g.), m. p. and mixed m. p. 231—233°.

(b) *With alkali.* When the amide (0·5 g.) was kept in N-sodium hydroxide (5 ml.) at room temperature for 2 days a clear yellow solution was obtained from which a pale yellow solid separated on acidification with N-hydrochloric acid (5 ml.). Extraction of the solid with sodium hydrogen carbonate solution left about 0·04 g. of solid, m. p. 173—175°, not depressed on admixture with the *trans*-amide. From the extract on acidification *trans*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (0·29 g.) separated as needles, m. p. and mixed m. p. 175—176°.

Hydrolysis of trans-*5-Phenyl-2-thiothiazolidine-4-carboxyamide.*—Acid or alkali under conditions similar to those used for the *cis*-isomer gave the *trans*-acid, m. p. 175—176°.

5-Benzylidenehexahydro-6-oxo-3-thio-1 : 2 : 4-triazine (VI).—(a) *Action of hydrazine hydrate on 4-benzylidene-2-thiothiazolid-5-one* (cf. Cook, Hunter, and Pollock [5]). A mixture of the thiazolidone (4·5 g.) and 90% hydrazine hydrate (6 ml.) in methanol (30 ml.) was kept at room temperature for 48 hr. The colourless solid (3·3 g.) that separated was removed and washed with methanol. It had m. p. 182—184° (decomp.) after gradually softening and becoming red from 132°. When this product [which is perhaps (VII)] was dissolved in hot water, hydrogen sulphide was evolved and the triazine separated as pale yellow needles, m. p. 244—246° (decomp.) (3·0 g.) raised to 263—265° (decomp.) on recrystallisation from acetic acid (Found: C, 54·7; H, 4·3; N, 19·3. Calc. for $C_{10}H_9ON_3S$: C, 54·8; H, 4·2; N, 19·2%) [lit., m. p. 251° (decomp.)].

(b) *Action of hydrazine hydrate on methyl* trans-*5-phenyl-2-thiothiazolidine-4-carboxylate.* A mixture of the ester (1 g.) and 90% hydrazine hydrate (1 ml.) was kept overnight at room temperature, then diluted with water (15 ml.) and warmed to 40°; the triazine (0·55 g.), m. p. 261° (decomp.), separated. The m. p., raised to 265° (decomp.) on recrystallisation from acetic acid, was not depressed on admixture with the previous sample.

The products formed by both methods gave the same methylated *derivative* when a sample (1·05 g.) suspended in N-sodium hydroxide (7 ml.) was shaken with methyl iodide (0·5 ml.). The derivative (0·7 g.) formed yellow needles, m. p. 164—165°, from methanol (Found: C, 57·1; H, 4·5; N, 18·3; S, 13·7. $C_{11}H_{11}ON_3S$ requires C, 56·7; H, 4·8; N, 18·0; S, 13·7%).

trans-*5-Phenyl-2-thiothiazolidine-4-carboxyhydrazide.*—To a solution of methyl *trans*-5-phenyl-2-thiothiazolidine-4-carboxylate (10 g.) in methanol (50 ml.) at 25°, 95% hydrazine hydrate (2·1 ml.) was added. Next day the colourless needles (7·0 g.) m. p. 189—191° (decomp.), that had separated were removed, washed with hot methanol, and dissolved in warm 2N-hydrochloric acid. The acid solution was filtered from a little insoluble material and cooled; trans-*5-phenyl-2-thiothiazolidine-4-carboxyhydrazide hydrochloride* which was precipitated, formed colourless needles, m. p. 206—207° (decomp.), from dilute hydrochloric acid (Found: C, 41·8; H, 4·4; N, 14·6. $C_{10}H_{12}ON_3S_2Cl$ requires C, 41·5; H, 4·2; N, 14·5%). When a solution of the hydrochloride was basified with sodium hydrogen carbonate trans-*5-phenyl-2-thiothiazolidine-4-carboxyhydrazide* was deposited. It was obtained as prisms, m. p. 195—196° (decomp.), on recrystallisation from ethanol (Found: C, 47·4; H, 4·5; N, 16·5. $C_{10}H_{11}ON_3S_2$ requires C, 47·4; H, 4·4; N, 16·6%).

The hydrazide (0·2 g.) in boiling alcohol (20 ml.) with benzaldehyde (0·15 ml.) gave the *benzylidene derivative* (0·22 g.), prisms, m. p. 225—226° (decomp.) (from ethanol) (Found: C, 60·0; H, 4·6; N, 12·4. $C_{17}H_{15}ON_3S_2$ requires C, 59·9; H, 4·4; N, 12·3%).

Diluting the filtrate of the original reaction product with water afforded the triazine (*ca.* 0·7 g.), m. p. and mixed m. p. 258—260° (decomp.).

trans-*5-Phenyl-2-thiothiazolidine-4-carbonylglycine.*—Powdered *trans*-5-phenyl-2-thiothiazolidine-4-carboxyhydrazide hydrochloride (2·8 g.) was suspended in a mixture of water (25 ml.), N-hydrochloric acid (5 ml.), and chloroform (20 ml.) at 0°, and sodium nitrite (0·8 g.) in a little

water was added slowly with stirring. When the solid had dissolved the chloroform layer was separated, washed with water, and dried ($MgSO_4$). To this extract glycine ethyl ester (1·35 g.) in chloroform (10 ml.) was added. After the mixture had been kept overnight at 0° the solvent was removed to leave an orange-red gum which was stirred for 3 hr. with N-sodium hydroxide (15 ml.). The resulting solution was then extracted with chloroform, and the aqueous layer acidified, to yield an oil which solidified when scratched (0·85 g.). Purified by dissolution in sodium hydrogen carbonate and re-acidification, it had m. p. 180—184° (decomp.) raised to 185—186° (decomp.) on recrystallisation from water. The product gave no depression on admixture with authentic *trans*-5-phenyl-2-thiothiazolidine-4-carbonylglycine (preceding paper) and gave the same *S*-benzylthiuronium salt, m. p. 183—184° (from alcohol) (Found: C, 51·8; H, 5·1; N, 12·2; S, 20·6. Calc. for $C_{20}H_{22}O_3N_4S_3$: C, 52·0; H, 4·8; N, 12·1; S, 20·8%).

The same product was obtained when the crude reaction mixture was hydrolysed for 1 hr. by a refluxing mixture of concentrated hydrochloric acid (4 ml.), water (20 ml.), and dioxan (10 ml.)

trans-2-*Methylthio*-5-*phenylthiazoline*-4-*carbonylglycine*.—A solution of the above acid (0·3 g.) in N-sodium hydroxide (2·2 ml.) was treated with methyl iodide (0·2 ml.) and shaken for 3 hr. The gum that was precipitated on neutralisation with dilute hydrochloric acid was dissolved in chloroform, and the dried solution was concentrated to small volume and diluted with a little light petroleum. The 2-methylthio-derivative which separated formed needles, m. p. and mixed m. p. 130—132°, on recrystallisation from chloroform–light petroleum.

trans-2-*Methylthio*-5-*phenylthiazoline*-4-*carboxylic Acid*.—To a solution of *trans*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (26 g.) in N-sodium hydroxide (230 ml.), methyl iodide (18·3 ml.) was added, and the mixture stirred for 2 hr. The resulting solution was acidified with dilute hydrochloric acid, and the precipitated gum extracted into chloroform. After being washed and dried, the extract was concentrated to small volume and treated with light petroleum; *trans*-2-methylthio-5-phenylthiazoline-4-carboxylic acid (22·5 g.) separated as prisms, m. p. 104—105°, not raised on recrystallisation from chloroform–light petroleum (Found: C, 52·1; H, 4·6; N, 5·7; S, 25·8. Calc. for $C_{11}H_{11}O_2NS_2$: C, 52·3; H, 4·4; N, 5·5; S, 25·3%) (Kashida and Yamanaka [7] give m. p. 104—105°). This compound depressed the m. p. of the isomeric methyl *trans*-5-phenyl-2-thiothiazolidine-4-carboxylate (m. p. 105—106°) on admixture and gave an S-*benzylthiuronium salt*, needles (from aqueous methanol), m. p. 158—159° (decomp.) (Found: C, 54·3; H, 5·3; N, 9·9. $C_{19}H_{21}O_2N_3S_3$ requires C, 54·5; H, 5·0; N, 10·0%). trans-2-*Methylthio*-5-*phenylthiazoline*-4-*carboxylic acid hydrochloride* (1·3 g.), formed when a solution of the acid (1·25 g.) in dry chloroform (15 ml.) was treated with dry hydrogen chloride, was obtained as platelets, m. p. 166—167°, on recrystallisation from alcohol–ether (Found: C, 45·3; H, 4·3; N, 5·0; Cl, 12·3. $C_{11}H_{12}O_2NS_2Cl$ requires C, 45·6; H, 4·2; N, 4·8; Cl, 12·3%). When the hydrochloride was shaken with water it became gummy and reverted to the free acid which was obtained solid by extraction into chloroform and precipitation with light petroleum.

Methyl trans-2-*methylthio*-5-*phenylthiazoline*-4-*carboxylate* was obtained as a pale yellow oil (8·3 g.), b. p. 136°/0·2 mm., when the above acid (9 g.) was esterified with diazomethane in ether (Found: C, 53·7; H, 5·2; N, 5·5. $C_{12}H_{13}O_2NS_2$ requires C, 54·0; H, 4·9; N, 5·2%).

trans-2-*Methylthio*-5-*phenylthiazoline*-4-*carboxhydrazide*.—*trans*-2-Methylthio-5-phenylthiazoline-4-carboxylic acid (10 g.) was esterified in ether with diazomethane, and the resulting oil dissolved in methanol (50 ml.) and treated with 95% hydrazine hydrate (4·5 ml.). When next day the solution was diluted with water the required hydrazide separated, on scratching, as needles (8·45 g.), m. p. 95—97°, raised to 99—100° on recrystallisation from aqueous methanol (Found: C, 49·9; H, 5·2; N, 15·8. $C_{11}H_{13}ON_3S_2$ requires C, 49·5; H, 4·9; N, 15·7%). The p-*nitrobenzylidene derivative* prepared in methyl alcohol was obtained as yellow prisms, m. p. 194°, from ethyl cellosolve–methanol (Found: C, 54·2; H, 3·7; N, 13·9. $C_{18}H_{16}O_3N_4S_2$ requires C, 54·0; H, 4·0; N, 14·0%).

trans-2-*Methylthio*-5-*phenylthiazoline*-4-*carbonylglycine Methyl Ester*.—A solution of the above hydrazide (1·35 g.) in N-hydrochloric acid (7·5 ml.) was stirred with chloroform (10 ml.) in an ice-bath while sodium nitrite (0·4 g.) in a little water was slowly added. The chloroform layer was then separated, washed with a little water, dried ($MgSO_4$), and treated with a solution of glycine methyl ester in chloroform prepared from the hydrochloride (1·5 g.). After being kept overnight the mixture was washed with a little water, dried, and evaporated. A solution of the resulting oil in ether gave, on scratching, *trans*-2-methylthio-5-phenylthiazoline-4-carbonylglycine methyl ester (0·35 g.), m. p. and mixed m. p. 80—81°.

cis-2-*Methylthio*-5-*phenylthiazoline*-4-*carboxylic Acid*.—A stirred solution of *cis*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (6 g.) in N-sodium hydroxide (53 ml.) was treated with methyl iodide (4·3 ml.). After 2 hr. chloroform (50 ml.) and concentrated hydrochloric acid (5 ml.) were added, and the mixture was stirred for a further 10 min. After being washed and dried the chloroform layer was concentrated to small volume and diluted with a little light petroleum; cis-2-*methylthio*-5-*phenylthiazoline*-4-*carboxylic acid* (3·1 g.) separated as needles, m. p. 137—138°, not raised on recrystallisation from chloroform–light petroleum (Found: C, 51·9; H, 4·3; N, 5·8%).

Methyl cis-2-*methylthio*-5-*phenylthiazoline*-4-*carboxylate* was obtained as colourless needles (from ether–light petroleum), m. p. 82—83°, when the *cis*-acid was esterified with diazomethane in the usual way (Found: C, 54·1; H, 5·5; N, 5·5%).

Reaction of Methyl cis-2-*Methylthio*-5-*phenylthiazoline*-4-*carboxylate with Hydrazine Hydrate*.—The ester (0·5 g.) in methanol (10 ml.) was treated with 90% hydrazine hydrate (1 ml.). When next day the solution was diluted with water, needles, m. p. 97—98°, of the *trans*-hydrazide separated. The m. p. was not depressed on admixture with a sample prepared from the *trans*-ester.

Reaction of cis-5-*Phenyl*-2-*thiothiazolidine*-4-*carboxylic Acid with Diazomethane*.—A suspension of the acid (1·5 g.) in ether was treated with an excess of diazomethane. Next day the crystals that had separated were removed (0·45 g.), to give needles, m. p. 125—125·5°, on recrystallisation from ether–methanol. The product was probably *methyl* cis-3-*methyl*-5-*phenyl*-2-*thiothiazolidine*-4-*carboxylate* (Found: C, 54·0; H, 4·5; N, 4·9%), $\lambda_{max.}$ (in EtOH) 275 mμ (ε 19310). From the original ether filtrate there was obtained on concentration methyl *cis*-2-methylthio-5-phenylthiazoline-4-carboxylate (0·58 g.), m. p. and mixed m. p. 80—81°.

Methyl trans-5-*Phenylthiazolidine*-4-*carboxylate*.—A solution in methanol (250 ml.) of the oily ester derived from *trans*-2-methylthio-5-phenylthiazoline-4-carboxylic acid (13 g.) and diazomethane was added to amalgamated aluminium (8 g.) at room temperature. After 3 days the alumina that had formed was removed and extracted with hot methanol in several portions (250 ml. total). The extracts were combined with the original reaction solution, and the whole was concentrated *in vacuo*, to leave methyl *trans*-5-phenylthiazolidine-4-carboxylate as a pale yellow oil which crystallised (scratching) (5·4 g.); m. p. 76—77°, unchanged on recrystallisation from methanol–ether (whence it was obtained as needles) (lit.,[7] m. p. 73°) (Found: C, 59·4; H, 5·9; N, 6·3. Calc. for $C_{11}H_{13}O_2NS$: C, 59·2; H, 5·9; N, 6·3%).

threo-*Phenylcysteine Methyl Ester Hydrochloride*.—A solution of methyl *trans*-5-phenylthiazolidine-4-carboxylate (2 g.) in boiling ethanol (20 ml.) was diluted with water (200 ml.) at 80°, and the mixture immediately treated with a solution of mercuric chloride (2·5 g.) in hot water (100 ml.). After the mixture had cooled to room temperature the white solid that had been precipitated was filtered off, washed with water, and dried (4·5 g.). It was then suspended in ethanol and decomposed with hydrogen sulphide. After removal of the mercuric sulphide the solution was evaporated to dryness, to leave *threo*-phenylcysteine methyl ester hydrochloride (2·2 g.), m. p. 174—176° (decomp.), raised to 184—185° (decomp.) on recrystallisation from alcohol–ether (Found: C, 48·6; H, 6·0; N, 5·7. Calc. for $C_{10}H_{14}O_2NSCl$: C, 48·5; H, 5·7; N, 5·7%).

threo-*Phenylcysteine Hydrochloride*.—The above methyl ester hydrochloride (1·14 g.) was heated under reflux with concentrated hydrochloric acid (2·5 ml.) and water (2·5 ml.) for 0·5 hr. On cooling, the *threo*-amino-acid hydrochloride slowly separated as leaflets (0·73 g.), m. p. 205—207° (decomp.), not raised on recrystallisation from propan-2-ol–ether (Found: C, 46·9; H, 5·5; N, 5·6; Cl, 15·2. Calc. for $C_9H_{12}O_2NSCl$: C, 46·3; H, 5·2; N, 6·0; Cl, 15·2%).

BEECHAM RESEARCH LABORATORIES LIMITED,
BROCKHAM PARK, BETCHWORTH, SURREY.

[*Received, July 7th*, 1958.]

XUM

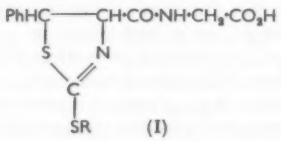
927. *Thiazolidines. Part III.*[1] *The Reaction of 2-Methylthio-5-phenylthiazoline-4-carboxylic Acid with Thionyl Chloride and Phosphorus Pentachloride.*

By D. O. Holland and P. Mamalis.

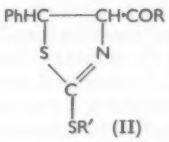
cis- or *trans*-2-Methylthio-5-phenylthiazoline-4-carboxylic acid (II; R = OH, R′ = Me) with thionyl chloride or phosphorus pentachloride gives a gum which with bases yields compounds believed to be α-(methylthio-thiocarbonylamino)cinnamic acid derivatives (VI).

A synthesis of *trans*-5-phenyl-2-thiothiazolidine-4-carbonylglycine (I; R = H) * and its *S*-methyl derivative (I; R = Me) from the 4-carboxylic acids (II; R = OH, R′ = H or Me respectively) by way of the hydrazides (II; R = NH·NH$_2$, R′ = H or Me) is described in the preceding paper, but the *cis*-peptide could not be obtained by this method. The acid chloride route to peptides was therefore explored.

trans-5-Phenyl-2-thiothiazolidine-4-carboxylic acid (II; R = OH, R′ = H) with thionyl chloride or phosphorus pentachloride in chloroform or benzene yielded dark oils which with aniline or ammonia furnished intractable gums.

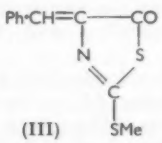


(I)

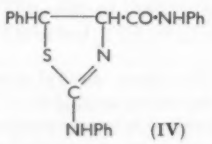


(II)

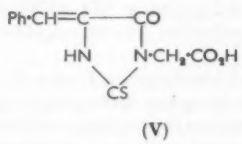
The corresponding *S*-methyl acid (II; R = OH, R′ = Me) with phosphorus pentachloride in benzene solution gave, besides a small quantity of 4-benzylidene-2-methylthiothiazolin-5-one (III), a gum which with aniline yielded a solid possessing the empirical formula for the required anilide (II; R = NHPh, R′ = Me). However, whereas the authentic anilide, prepared by the action of aniline on the azide derived from *trans*-2-methylthio-5-phenylthiazoline-4-carboxyhydrazide (II; R = NH·NH$_2$, R′ = Me),[1] on further reaction with warm aniline yielded compound (IV), the isomeric product from the phosphorus pentachloride reaction remained unchanged (cf. Cook, Elvidge, and Shaw,[2] who converted ethyl 2-ethylthio-5 : 5-dimethylthiazoline-4-carboxylate into the 2-anilino-derivative in this way). The ultraviolet absorption was also quite different.



(III)



(IV)



(V)

The phosphorus pentachloride reaction product, when treated with glycine methyl ester, gave two solids after alkaline hydrolysis. One proved to be the thiohydantoin (V),[1] probably derived from the benzylidene derivative (III), while the other, a white solid soluble in aqueous sodium hydrogen carbonate, gave correct analyses for the required glycyl-peptide (I; R = Me), but again its properties precluded this structure and its methyl ester (prepared with diazomethane) differed from *trans*-2-methylthio-5-phenylthiazoline-4-carbonylglycine methyl ester.

The *S*-methyl acid (II; R = OH, R′ = Me) with thionyl chloride gave similar results.

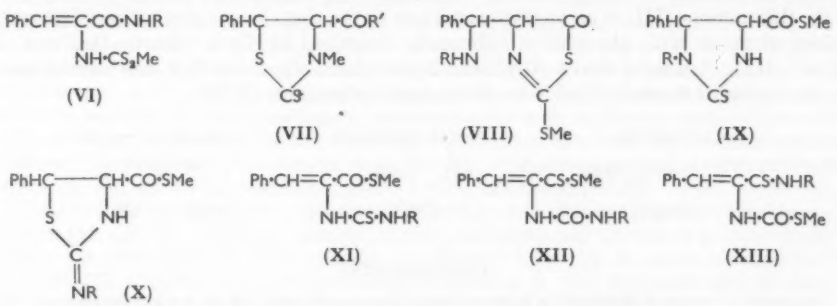
* See footnote on p. 4584.

[1] Parts I and II, preceding papers.

[2] Cook, Elvidge, and Shaw, *J.*, 1949, 2369.

Thionyl chloride, added to the acid in dry benzene at room temperature, yielded a deliquescent solid which appeared to be a loose complex of the thiazoline with thionyl chloride since *in vacuo* it reverted to the starting material. The hydrochloride of the thiazoline was found to be quite stable under these conditions.[1] When the reaction mixture was heated, the solid dissolved with evolution of sulphur dioxide and hydrogen chloride, and a good yield of 4-benzylidene-2-methylthiothiazolin-5-one (III) was obtained. When, however, the reaction was carried out in chloroform the gummy product contained none of the thiazolinone (III): after treatment with aniline or glycine ester it gave the same products as were obtained from the phosphorus pentachloride reaction. Similarly, when the gum was allowed to react with ammonia a product isomeric with the required amide (II; R = NH_2, R′ = Me) was obtained. The same products also arose from *cis*-2-methylthio-5-phenylthiazoline-4-carboxylic acid (II; R = OH, R′ = Me).

The ammonia reaction product was soluble in concentrated but insoluble in dilute hydrochloric acid and with acetic anhydride yielded a monoacetyl derivative. On hydrolysis with either acid or alkali it yielded an acid isomeric with the thiazoline acid (II; R = OH, R′ = Me) and affording a different methyl ester on treatment with diazomethane. This ester was also obtained directly from the gum by reaction with methanol. This product and the other derivatives of the gum described above, with the exception of that from aniline, have very similar ultraviolet absorption spectra which differ markedly from those of the isomers possessing the 2-methylthio-5-phenylthiazoline structure (no maximum).

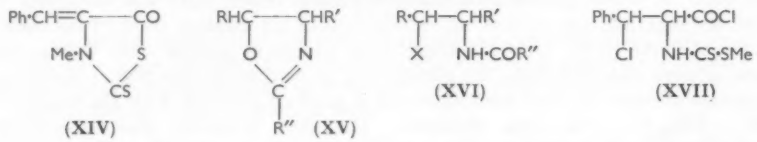


Of the possible structures (VI—XIII) for the new amino-derivatives, structures (IX—XII) appeared unlikely since methanethiol was not released on comparatively mild acid hydrolysis (cf. Doyle, Holland, and Nayler [3]): carbamic esters derived from amino-acids resist acid hydrolysis (cf. Cagnon and Boivin [4]) and hence structures (VI) and (XIII) would not be expected to lose methanethiol under these conditions. The loss of the amino-group on acid or alkaline hydrolysis to yield an acid which with diazomethane gave the same methyl ester as that obtained directly from the gum eliminated structure (VIII) and indicated the presence of an amide group which brought formulæ (VI), (VII; R′ = NHR), and (XIII) into consideration. The thioamide (XIII) appeared unlikely in comparison with the normal amide (VI) since it would have been expected to lose a sulphur atom on hydrolysis. The structure (VII) was eliminated by synthesis of the authentic acid, methyl ester, and amide whose ultraviolet spectra differed from those of the compounds obtained from the gum. The acid and the amide were prepared by the ring-turning of 4-benzylidene-3-methyl-2-thiothiazolid-5-one (XIV) with alkali and ammonia respectively,[5] and the methyl ester was made from the acid by reaction with diazomethane. The amide was also obtained from the ester by reaction with ammonia.

The methyl ester (VII; R′ = OMe), m. p. 107—108°, had an ultraviolet spectrum

[3] Doyle, Holland, and Nayler, *J.*, 1955, 2265.
[4] Cagnon and Boivin, *Canad. J. Res.*, 1948, **26**, *B*, 503.
[5] (*a*) Cook and Cox, *J.*, 1949, 2342; (*b*) Siddappa, Thesis, London, 1950.

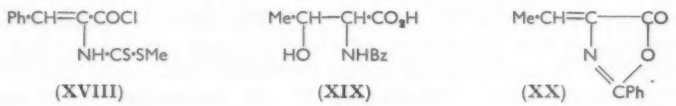
almost identical with that of the suspected methyl 3-methyl-5-phenyl-2-thiothiazolidine-4-carboxylate, m. p. 125—125·5°, obtained by the action of diazomethane on *cis*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (II; R = OH, R′ = H).[1] Evidently ring-turning of 4-benzylidene-3-methyl-2-thiothiazolid-5-one with alkali or ammonia leads to *trans*-*N*-methylated thiazolidines (VII; R′ = OH or NH_2).



(XIV) (XV) (XVI) (XVII)

Attempts to synthesize compounds with the structure (VI) by alternative routes were not made.

The formation of the thiazolinone (III) by the action of phosphorus pentachloride or thionyl chloride on the thiazoline acid (II; R = OH, R′ = Me) must involve fission of the thiazoline ring. Fry [6] has shown that analogous oxazolines (XV) open under the influence of hydrogen halides to give β-halogeno-α-amido-compounds (XVI). It is possible that a similar reaction occurs with the thiazoline (II; R = OH, R′ = Me) to give an intermediate (XVII) which loses one molecule of hydrogen chloride to give the unsaturated acid chloride (XVIII). Under the influence of thionyl chloride or phosphorus pentachloride this may partly cyclise to the thiazolinone (III) in an analogous manner to the ring closure of ethyl carboxymethyldithiocarbamate with phosphorus tribromide described by Cook, Harris, Heilbron, and Shaw.[7] It is noteworthy that 4-ethylidene-2-phenyloxazolin-5-one (XX) has been obtained [8] by the action of thionyl chloride on *N*-benzoyl*allo*threonine (XIX).



(XVIII) (XIX) (XX)

Experimental

Reaction of trans-2-*Methylthio-5-phenylthiazoline-4-carboxylic Acid with Phosphorus Pentachloride.*—The acid (2·5 g.) and phosphorus pentachloride (2·1 g.) in dry benzene (20 ml.) were heated under reflux for 1·5 hr. The solvent was then removed *in vacuo* and the resulting partially crystalline residue crystallised from benzene–light petroleum, to yield 4-benzylidene-2-methylthiothiazolin-5-one (0·4 g.), m. p. 93—97°. On recrystallisation from the same solvents it was obtained as yellow needles, m. p. 97° alone and when mixed with an authentic specimen (see below). (Found: C, 55·9; H, 4·2; N, 6·1. Calc. for $C_{11}H_9ONS_2$: C, 56·2; H, 3·9; N, 6·0%).

To the mother-liquor from the crystallisation of the above compound aniline (1 ml.) was added. After 2 hr. the solution was extracted with dilute hydrochloric acid, washed with water, and dried ($MgSO_4$). It was then concentrated to small volume and treated with light petroleum; a solid (0·3 g.) separated, as yellow prisms, m. p. 152—153°, probably α-(*methylthio-thiocarbonylamino*)*cinnamanilide* (VI; R = Ph) (Found: C, 62·3; H, 4·8; N, 8·3; S, 19·6. $C_{17}H_{16}ON_2S_2$ requires C, 62·3; H, 4·9; N, 8·5; S, 19·5%), $\lambda_{max.}$ (in EtOH) 287 mμ (ε 18,235).

The mother-liquors from a similar reaction were treated with glycine methyl ester (prepared from 1·65 g. of the ester hydrochloride) and triethylamine (2·1 ml.) in chloroform (10 ml.) and kept for 2 hr. The solution was then extracted with dilute hydrochloric acid, washed with water, dried, and evaporated. The sticky residue was treated with N-sodium hydroxide (20 ml.) for 2 hr. at room temperature. The resulting sticky yellow-brown solid was removed and crystallised from alcohol, to give 4-benzylidene-2-methylthiothiazolin-5-one, m. p. 96—97°.

[6] Fry, *J. Org. Chem.*, 1949, **14**, 887; 1950, **15**, 438.
[7] Cook, Harris, Heilbron, and Shaw, *J.*, 1948, 1056.
[8] Pfister, Robinson, Shabica, and Tishler, *J. Amer. Chem. Soc.*, 1948, **70**, 2297; 1949, **71**, 1101.

The remaining alkaline solution was extracted with chloroform and acidified with dilute hydrochloric acid. On addition of chloroform to this acid solution a solid separated (0·18 g.). It was crystallised by dissolving it in N-sodium hydroxide and acidifying the solution carefully at 85°, 4-benzylidene-4 : 5-dihydro-2-mercapto-5-oxoglyoxalin-1-ylacetic acid separating as pale yellow needles, m. p. 255°, alone and when mixed with an authentic specimen [1] (Found: C, 55·2; H, 4·0; N, 10·7. Calc. for $C_{12}H_{10}O_3N_2S$: C, 55·1; H, 3·9; N, 10·7%).

The chloroform layer from the acidified solution was washed with water, dried, and concentrated to small volume. On addition of light petroleum a small quantity of a white solid slowly separated, being obtained as needles, m. p. 184—185°, on recrystallisation from chloroform–light petroleum. It was probably N-[α-(*methylthio-thiocarbonylamino*)*cinnamoyl*]*glycine* (VI; R = $CH_2{\cdot}CO_2H$) (Found: C, 50·6; H, 4·3; N, 9·2; S, 20·5. $C_{13}H_{14}O_3N_2S_2$ requires C, 50·4; H, 4·6; N, 9·0; S, 20·6%), $\lambda_{max.}$ (in EtOH) 304 mμ (ε 12,620).

Esterification of this compound with diazomethane in ether gave the *methyl ester*, needles, m. p. 86—87° (from ether–light petroleum) (Found: C, 51·7; H, 4·7; N, 9·5. $C_{14}H_{16}O_3N_2S_2$ requires C, 51·9; H, 5·0; N, 8·7%). It depressed the m. p. of *trans*-2-methylthio-5-phenylthiazoline-4-carbonylglycine methyl ester [1] (m. p. 80—81°) by 20°.

4-Benzylidene-2-methylthiothiazolin-5-one.—4-Benzylidene-2-thiothiazolid-5-one (2·5 g.) was shaken for 10 min. with methyl iodide (1·1 ml.) in N-sodium hydroxide (11·5 ml.). The product was removed and recrystallised from methyl alcohol as yellow prismatic needles, m. p. 96—97° (1·6 g.). The same product was obtained when methyl sulphate was used instead of methyl iodide (Cook and Cox [5a] gave m. p. 99—100° for this compound, using methyl iodide for its preparation; Cook and Pollock [9] used methyl sulphate and gave m. p. 124°).

trans-2-*Methylthio-5-phenylthiazoline-4-carboxyanilide.*—A solution of *trans*-2-methylthio-5-phenylthiazoline-4-carboxyhydrazide [1] (1·35 g.) in N-hydrochloric acid (7·5 ml.) and water (12·5 ml.) was stirred at 0° in the presence of chloroform (10 ml.) while sodium nitrite (0·4 g.) in a little water was added during 5 min. The chloroform layer was separated, washed with a little ice-water, dried ($MgSO_4$), and treated with aniline (0·5 ml.). Next day the solvent was removed to leave an oil which was passed in benzene down a short alumina column; the *anilide* (0·3 g.) slowly separated from the benzene eluate on addition of a little ethyl acetate and light petroleum. It was obtained as needles, m. p. 83—84°, from the latter pair of solvents (Found: C, 62·2; H, 5·0; N, 8·9%), and had $\lambda_{max.}$ (in EtOH) 237 mμ (ε 24,750).

2-Anilino-5-phenylthiazoline-4-carboxyanilide (0·88 g.) was obtained when the above reaction was repeated and the chloroform solution containing aniline was heated on a steam-bath for 20 min. On concentration of the solution the product separated as cream-coloured prisms, m. p. 171—173°. It was obtained as colourless needles, m. p. 178°, from methanol (Found: C, 70·7; H, 5·2; N, 11·3. $C_{22}H_{19}ON_3S$ requires C, 70·8; H, 5·1; N, 11·3%).

Reaction of trans-2-*Methylthio-5-phenylthiazoline-4-carboxylic Acid with Thionyl Chloride.*—(a) *In benzene.* A solution of the acid (2·5 g.) in dry benzene (100 ml.) was concentrated to 50 ml. to remove last traces of moisture and then treated at room temperature with thionyl chloride (distilled over quinoline and linseed oil) (3·0 ml.). The precipitated *solid* was removed after 3 hr. at 10° and washed with benzene; it had m. p. 116° (decomp.) after softening from 101° (2·35 g.) and when kept in a desiccator developed an odour of thionyl chloride; the solid then gave the same analysis as the starting material (Found: C, 52·4; H, 4·4; N, 5·3. Calc. for $C_{11}H_{11}O_2NS_2$: C, 52·3; H, 4·4; N, 5·5%). Use of 6 ml. of thionyl chloride and heating under reflux for 1 hr. gave a clear solution; removal of the solvent left a syrup which solidified on the addition of a little methyl alcohol; the solid (1·8 g.) on recrystallisation from methyl alcohol gave needles, m. p. 98—99°, not depressed when mixed with 4-benzylidene-2-methylthiothiazolin-5-one.

(b) *In chloroform.* A mixture of the acid (1·25 g.) and pure thionyl chloride (3 ml.) in dry chloroform (5 ml.) was heated under reflux for 1 hr. A solid separated initially but this dissolved after about 15 min. Removal of the solvent left a gum which was dissolved in chloroform (5 ml.) and treated with aniline (2 ml.). Next day the mixture was extracted with dilute hydrochloric acid, and the solvent layer washed with water, dried, and concentrated. On the addition of light petroleum α-(methylthio-thiocarbonylamino)cinnamanilide separated as yellow prisms (0·90 g.), m. p. 150—151°, not depressed on admixture with the product from the phosphorus pentachloride reaction.

[9] Cook and Pollock, *J.*, 1950, 1898.

A solution of the gum from a similar experiment (using 1·5 g. of acid) in chloroform (10 ml.) was treated with glycine methyl ester hydrochloride (1·26 g.) and triethylamine (7 ml.) in chloroform (15 ml.). After 3 hr. the solution was extracted with dilute hydrochloric acid, washed with water, and dried. Removing the solvent *in vacuo* gave a gum which was stirred with N-sodium hydroxide (15 ml.) at room temperature for 1 hr. Next day the resulting solution was extracted with chloroform and acidified with N-hydrochloric acid (18 ml.). On the addition of a little chloroform *N*-[α-(methylthio-thiocarbonylamino)cinnamoylglycine (1·1 g.) separated as a cream-coloured solid, soluble in aqueous sodium hydrogen carbonate solution. When recrystallised from water containing a little alcohol it was obtained as needles, m. p. 191°, not depressed on admixture with the product from the phosphorus pentachloride reaction.

α-(*Methylthio-thiocarbonylamino*)*cinnamamide*.—When the gum from the reaction of *trans*-2-methylthio-5-phenylthiazoline-4-carboxylic acid (1·25 g.) with thionyl chloride in chloroform solution was treated with ammonia (*d* 0·88; 5 ml.) for 16 hr. and a little methyl alcohol then added, a solid was obtained which on recrystallisation from aqueous methanol yielded needles, m. p. 122—124° (0·55 g.), probably α-(*methylthio-thiocarbonylamino*)*cinnamamide* (Found: C, 52·5; H, 4·1; N, 10·8; S, 24·9. $C_{11}H_{12}ON_2S_2$ requires C, 52·4; H, 4·8; N, 11·1; S, 25·4%), $\lambda_{max.}$ (in EtOH) 304 mμ (ε 11,485).

When this amide (0·5 g.) was heated under reflux for 15 min. with acetic anhydride (4 ml.) in the presence of 1 drop of concentrated sulphuric acid, then further on a steam-bath for 45 min. a brown solution was obtained from which the addition of water afforded a *monoacetyl derivative*, cream-coloured needles (0·34 g.) (from aqueous methanol), m. p. 97—98° (Found: C, 53·5; H, 4·4; N, 9·5; S, 21·6. $C_{13}H_{14}O_2N_2S_2$ requires C, 53·1; H, 4·8; N, 9·5; S, 21·8%).

trans-2-*Methylthio-5-phenylthiazoline-4-carboxyamide*.—A mixture of *trans*-5-phenyl-2-thiothiazolidine-4-carboxyamide (0·5 g.) and methyl iodide (0·5 ml.) in N-sodium hydroxide (2·5 ml.) was kept at 0° for 16 hr. and extracted with chloroform. After being washed and dried the chloroform extract was concentrated to small volume and treated with light petroleum; *trans*-2-methylthio-5-phenylthiazoline-4-carboxyamide separated as needles, m. p. 92—93°, not raised on recrystallisation from the same solvent mixture (Found: C, 52·2; H, 5·0; N, 11·6%). This corresponds to Cook, Hunter, and Pollock's α-form [10]

α-(*Methylthio-thiocarbonylamino*)*cinnamic Acid*.—The corresponding amide (1·0 g.) was heated under reflux for 5 hr. with concentrated hydrochloric acid (5·0 ml.), acetic acid (5·0 ml.), and water (5·0 ml.). The resulting mixture was cooled and diluted with water; on scratching, the required *acid* (0·75 g.) separated, having m. p. 140—141°, unchanged on recrystallisation from aqueous methanol whence it was obtained as pale yellow prisms (Found: C, 52·2; H, 3·8; N, 5·6; S, 24·9. $C_{11}H_{11}O_2NS_2$ requires C, 52·3; H, 4·4; N, 5·5; S, 25·3%), $\lambda_{max.}$ (in EtOH) 303 mμ (ε 10,900).

After the amide (1·0 g.) had been hydrolysed with sodium hydroxide (1·5 g.) under reflux for 4 hr. in 50% methanol (20 ml.) the *sodium salt* of the acid slowly separated as plates, m. p. > 290° when the product was kept at room temperature (Found: C, 47·6; H, 3·3; N, 5·2. $C_{11}H_{10}O_2NS_2Na$ requires C, 48·0; H, 3·7; N, 5·1%). When a solution of the sodium salt in warm water was acidified the free acid separated, having m. p. and mixed m. p. 139—140°.

Methyl α-(*Methylthio-thiocarbonylamino*)*cinnamate*.—The gum from reaction of *trans*-2-methylthio-5-phenylthiazoline-4-carboxylic acid (2·5 g.) with thionyl chloride in chloroform solution was dissolved in dry methyl alcohol (15 ml.). When next day water was added to the solution, the *methyl ester* separated (1·4 g.); from aqueous methanol it formed cream-coloured needles, m. p. 64—66° (Found: C, 54·4; H, 5·2; N, 5·2; S, 24·3. $C_{12}H_{13}O_2NS_2$ requires C 54·0; H, 4·9; N, 5·3; S, 24·0%).

The same ester was obtained from the acid by esterification with diazomethane in ethyl acetate, as needles (from ether–light petroleum), m. p. and mixed m. p. 66—67° (Found: C, 54·2; H, 4·7; N, 5·6%).

Reaction of cis-2-*Methylthio-5-phenylthiazoline-4-carboxylic Acid with Thionyl Chloride*.—The *cis*-acid (2·5 g.) and pure thionyl chloride (6 ml.) were heated under reflux in chloroform (10 ml.) for 30 min., then evaporated to a gum. To a solution of this in chloroform (10 ml.), glycine ethyl ester hydrochloride (1·35 g.) was added followed by triethylamine (7 ml.) in chloroform (15 ml.). After 3 days the mixture was extracted with dilute hydrochloric acid. The chloroform layer was then washed with water, dried, and concentrated *in vacuo* to leave a gum which

[10] Cook, Hunter, and Pollock, *J.*, 1950, 1892

XUM

was hydrolysed by stirring it with N-sodium hydroxide (15 ml.) for 1 hr. After extraction of a small residue with chloroform the solution was acidified, a gum separating which solidified. It recrystallised from aqueous alcohol as buff needles, m. p. 181—182° (0·6 g.), not depressed on admixture with *N*-[α-methylthio-thiocarbonylamino)cinnamoyl]glycine.

When the gum from 1·25 g. of the *cis*-acid was allowed to react with ammonia a product (0·7 g.) was obtained, having m. p. 123°, alone and when mixed with α-(methylthio-thiocarbonylamino)cinnamamide.

Similar reaction of the gum with aniline yielded the anilide, m. p. 148—152°, not depressed on admixture with the product obtained from *trans*-2-methylthio-5-phenylthiazoline-4-carboxylic acid.

Methyl trans-3-*Methyl*-5-*phenyl*-2-*thiothiazolidine*-4-*carboxylate* was obtained from the corresponding acid (Cook and Cox [5a]) by reaction with diazomethane in ether, as needles (from methyl alcohol), m. p. 107—108° (Found: C, 53·7; H, 4·8; N, 5·5%), $\lambda_{max.}$ (in EtOH) 276 mμ (ε 16,400), or by the action of refluxing methyl alcohol in the presence of a little sulphuric acid.

trans-3-*Methyl*-5-*phenyl*-2-*thiothiazolidine*-4-*carboxyamide*.—4-Benzylidene-3-methyl-2-thiothiazolidin-5-one (2·0 g.) and ammonia (*d* 0·88; 7 ml.) were heated on a steam-bath for 2 hr. To the yellow oil that was formed methyl alcohol was added. On cooling, the required amide separated (1·5 g). It was obtained as needles, m. p. 131—132°, from methanol (cf. Siddappa [5b]) (Found: C, 52·5; H, 4·3; N, 11·3%), $\lambda_{max.}$ (in EtOH) 277 mμ (ε 17,000.) The amide was also obtained by heating a solution of the methyl ester (1·0 g.) described above in methyl alcohol (15 ml.) with ammonia (*d* 0·88; 6 ml.) for several hours.

BEECHAM RESEARCH LABORATORIES LIMITED,
BROCKHAM PARK, BETCHWORTH, SURREY.

[*Received, July 7th*, 1958.]

---

928. *Thiazolidines. Part IV.*[1] *Further Reactions of 2-Methylthio-5-phenylthiazoline-4-carboxylic Acid.*

By D. O. HOLLAND and P. MAMALIS.

cis- and *trans*-2-Oxo-5-phenylthiazolidine-4-carboxylic acid have been prepared from the corresponding 2-methylthio-acids by way of *erythro*- and *threo*-*S*-(methylthio-carbonyl)-β-phenylcysteine hydrochloride (II) and by the action of chloroacetic acid on the respective 2-methylthiothiazoline acids. The action of hydrogen peroxide on the *trans*-2-methylthiothiazoline acid gave (probably) 5-phenylthiazole-4-carboxylic acid, as well as the expected thiazolidone. This acid, together with phenylpyruvic acid, also arose by the action of alkali on the *trans*-2-methylthio-acid (I; R = Me, R′ = H). Methyl *cis*-2-oxo-5-phenylthiazolidine-4-carboxylate has been converted into the *trans*-acids.

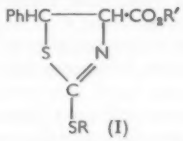
WHEREAS hydrolysis of methyl *cis*- and *trans*-5-phenyl-2-thiothiazolidine-4-carboxylate (I; R = H, R′ = Me) * with hydrochloric acid gives the respective acids which are therefore stable to this treatment (Part II of this series [1]), the corresponding 2-methylthiothiazoline esters and acids (I; R = Me, R′ = H; and R = R′ = Me) have now been found to yield the two diastereoisomeric *S*-(methylthio-carbonyl)-β-phenylcysteine hydrochlorides (II), as in the conversion of 2-benzylthiothiazoline-4-carboxylic acid into *S*-(benzylthio-carbonyl)cysteine hydrochloride (Crawhall and Elliott [2]). In accord with the suggestions of Sicher *et al.*[3] it is probable the amino-acids (II) arising from the *cis*- and the *trans*-thiazoline have the *erythro*- and the *threo*-configuration respectively.

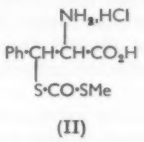
With aqueous-alcoholic sodium hydroxide at room temperature the two forms of the

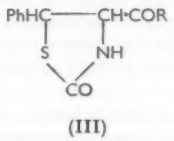
* See footnote on p. 4584.

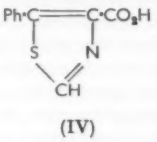
[1] Parts II and III, preceding papers.
[2] Crawhall and Elliott, *J.*, 1951, 2071.
[3] Sicher, Svoboda, and Farkas, *Coll. Czech. Chem. Comm.*, 1955, **20**, 1439.

amino-acid (II) likewise behaved similarly to *S*-(benzylthio-carbonyl)cysteine hydrochloride, to give two forms of 2-oxo-5-phenylthiazolidine-4-carboxylic acid (III; R = OH)


(I)


(II)


(III)


(IV)

The derived methyl esters of these two acids (III; R = OMe), on hydrolysis with hot dilute hydrochloric acid, reverted to the corresponding acids without inversion, but as in the case of the 2-thio-analogues (I; R = H, R′ = Me) [1] hydrolysis with cold aqueous-alcoholic sodium hydroxide caused inversion of the higher-melting to the lower-melting form.

That the higher- and the lower-melting form of the oxothiazolidine acid (III; R = OH) corresponded to the *cis*- and the *trans*-form respectively of the 2-methylthiothiazoline ester (I; R = R′ = Me) from which they were derived thus appeared likely and was confirmed by the preparation of the two oxothiazolidine acids by treatment of *cis*- and *trans*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (I; R = R′ = H) with hot aqueous chloroacetic acid.[4] Similar treatment of *cis*-5-phenyl-2-thiothiazolidine-4-carboxyamide with chloroacetic acid likewise gave the corresponding *cis*-oxothiazolidine amide (III; R = NH_2), but the *trans*-amide yielded only the free acid (II; R = OH). However, the required product was obtained by the action of aqueous ammonia on the *trans*-ester (III; R = OMe) or of thionyl chloride on the oxothiazolidine acid followed by treatment of the gummy product with ammonia. The corresponding 2-thio-acid (I; R = R′ = H) gave only an intractable gum in this reaction.[1]

Cook, Harris, and Heilbron [5] reported that a 2-oxo-5-phenylthiazolidine-4-carboxylic acid was formed through the 2-ethylthiothiazoline acid (I; R = Et, R′ = H) when 4-benzylidene-2-ethylthiothiazol-5-one was heated with aqueous-alcoholic sodium hydroxide. The m. p. of their product was, however, different from that of either the *cis*- or the *trans*-oxothiazolidine acids described above, and using 4-benzylidene-2-methylthiothiazol-5-one [1] we obtained *trans*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (I; R = R′ = H). Further, when 2-methylthio-5-phenylthiazoline-4-carboxylic acid (*trans*-form used) is heated under reflux with N-sodium hydroxide, ammonia and methanethiol are evolved to yield, after acidification, a product giving analytical figures for 5-phenylthiazole-4-carboxylic acid (IV) together with phenylpyruvic acid.

Cook, Harris, Pollock, and Swan [6] obtained a compound, m. p. 225° (decomp.), considered to be 5-phenylthiazole-4-carboxylic acid hydrochloride, by heating triethylammonium 5-phenyl-2-thiothiazolidine-4-thiocarboxylate with concentrated hydrochloric acid. The suspected 5-phenylthiazole-4-carboxylic acid obtained by us, however, could not be converted into a hydrochloride.

Conversion of 5-substituted 2-thiothiazolidine-4-carboxylic acids and esters into their corresponding 2-oxo-analogues by alkaline hydrogen peroxide has been reported by Cook *et al.*[6,7] and by Kashida and Yamanaka.[8] In our hands good yields of the required 2-oxo-5-phenylthiazolidine-4-carboxylic acid were sometimes obtained in this way, but on other occasions considerable quantities of 5-phenylthiazole-4-carboxylic acid were also isolated. When alkaline potassium permanganate was used instead of hydrogen peroxide, only the thiazole was obtained. The corresponding 2-oxo-5-phenylthiazolidine-4-carboxylic acid was unaffected by this treatment, so it was not an intermediate in the conversion.

[4] Cf. Johnson and O'Brien, *J. Biol. Chem.*, 1912, **12**, 205.
[5] Cook, Harris, and Heilbron, *J.*, 1948, 1060.
[6] Cook, Harris, Pollock, and Swan, *J.*, 1950, 1947.
[7] Cook, Elvidge, and Shaw, *J.*, 1949, 2367.
[8] Kashida and Yamanaka, *J. Pharm. Soc. Japan*, 1953, **73**, 953 (*Chem. Abs.*, 1954, **48**, 11394).

XUM

Experimental

S-(*Methylthio-carbonyl*)-β-*phenylcysteine.*—*trans*-2-Methylthio-5-phenylthiazoline-4-carboxylic acid (1·25 g.) was heated with concentrated hydrochloric acid (10 ml.) and water (10 ml.) under reflux for 1 hr. threo-S-(*Methylthio-carbonyl*)-β-*phenylcysteine hydrochloride* (1·35 g.) separated. It formed colourless needles, m. p. 183—184° (decomp.), from alcohol–light petroleum (Found: C, 43·0; H, 5·0; N, 4·2; S, 21·5; Cl, 11·0. $C_{11}H_{14}O_3NS_2Cl$ requires C, 43·0; H, 4·6; N, 4·6; S, 20·8; Cl, 11·5%).

The same product was obtained when the corresponding thiazoline methyl ester was heated with aqueous hydrochloric acid.

When a solution of the hydrochloride in aqueous sodium hydrogen carbonate was carefully neutralised with dilute hydrochloric acid the free *amino-acid* separated, which was obtained as colourless needles, m. p. 164—168° (decomp.), from aqueous alcohol (Found: C, 49·3; H, 5·0; N, 5·7; S, 23·2. $C_{11}H_{13}O_3NS_2$ requires C, 48·8; H, 4·8; N, 5·2; S, 23·6%). The product gave a positive ninhydrin test for an α-amino-acid but a negative result in the nitroprusside and the iodine–sodium azide test for thiol groups.

trans-2-*Oxo*-5-*phenylthiazolidine*-4-*carboxylic Acid.*—(a) *From the* threo-S-(*methylthio-carbonyl*)-β-*phenylcysteine hydrochloride.* A suspension of the acid hydrochloride (1·0 g.) in alcohol (30 ml.) was treated with N-sodium hydroxide (10 ml.), a clear solution being formed. After 2 hr. the mixture was neutralised with N-hydrochloric acid and concentrated to small volume; *trans*-2-oxo-5-phenylthiazolidine-4-carboxylic acid separated as plates, m. p. 192—194° (decomp.), unchanged on recrystallisation from hot water [lit.,[8] m. p. 193—195° (decomp.)] (Found: C, 54·0; H, 4·1; N, 6·0. Calc. for $C_{10}H_9O_3NS$: C, 53·8; H, 4·1; N, 6·3%). The S-*benzylthiuronium salt* prepared in the usual way was obtained as colourless needles, m. p. 130—132° (after drying at 78°/3 mm.), from aqueous methanol (Found: C, 54·7; H, 5·6; N, 10·4. $C_{18}H_{19}O_3N_3S_2,CH_3{\cdot}OH$ requires C, 54·2; H, 5·5; N, 10·0%).

(b) *From* trans-5-*phenyl*-2-*thiothiazolidine*-4-*carboxylic acid.* The acid (2 g.) and chloroacetic acid (4 g.) were heated in water (20 ml.) under reflux for 2 hr. After several days at room temperature the precipitate (1·4 g.) was removed and recrystallised from water, as needles, m. p. and mixed m. p. 194—195° (decomp.).

Methyl trans-2-*oxo*-5-*phenylthiazolidine*-4-*carboxylate* was obtained by refluxing the acid (2·0 g.; prepared by method (b) with methyl alcohol (30 ml.) and concentrated sulphuric acid (0·5 ml.) for 2 hr., as needles, m. p. 93—94° (from aqueous methanol) (Found: C, 55·5; H, 4·9; N, 5·6. $C_{11}H_{11}O_3NS$ requires C, 55·8; H, 4·7; N, 5·9%). It was also obtained from the acid prepared by the former method described above by treatment with diazomethane in ethyl acetate, as prisms (from ethyl acetate–light petroleum), m. p. and mixed m. p. 94—95°.

Hydrolysis of Methyl trans-2-*Oxo*-5-*phenylthiazolidine*-4-*carboxylate.*—(a) *With acid.* When the ester (1·0 g.) was heated under reflux for 1 hr. in concentrated hydrochloric acid (5 ml.) and water (7 ml.) the *trans*-acid (0·9 g.), m. p. 192—194° (decomp.), was obtained on cooling of the solution. It did not depress the m. p. of an authentic specimen.

(b) *With alkali.* Similarly the *trans*-acid (0·4 g.), m. p. 192—193° (decomp.), was obtained when the ester (0·5 g.) was kept in a mixture of methyl alcohol (3 ml.) and N-sodium hydroxide (3 ml.) at room temperature for 16 hr. It separated as prisms when the solution was acidified with N-hydrochloric acid.

cis-2-*Oxo*-5-*phenylthiazolidine*-4-*carboxylic Acid.*—(a) *Via* erythro-S-(*methylthio-carbonyl*)-β-*phenylcysteine hydrochloride. cis*-2-Methylthio-5-phenylthiazoline-4-carboxylic acid (2 g.) was heated under reflux in 6N-hydrochloric acid (30 ml.) for 1 hr. erythro-S-(*Methylthio-carbonyl*)-β-*phenylcysteine hydrochloride* (1·75 g.) that separated was removed after cooling. It had m. p. 179—180° (decomp.), raised to 185—186° (decomp.) on recrystallisation from alcohol–ether (Found: C, 43·0; H, 5·3; N, 4·6. $C_{11}H_{14}O_3NS_2Cl$ requires C, 43·0; H, 4·6; N, 4·6%). It depressed slightly the m. p. of the *threo*-amino-acid hydrochloride on admixture. To a suspension of this compound in alcohol (50 ml.) N-sodium hydroxide (50 ml.) was added. Next day a trace of insoluble material was removed, and the solution concentrated *in vacuo* to small volume and acidified with concentrated hydrochloric acid, cis-2-*oxo*-5-*phenylthiazolidine*-4-*carboxylic acid* separating as cream-coloured leaflets (1·05 g.), m. p. 219—220° (decomp.), not depressed on admixture with a sample prepared by the method described below. The S-*benzylthiuronium salt* was obtained as colourless needles (from methanol), m. p. 242—244° (decomp.) (Found: C, 55·6; H, 5·1; N, 10·7. $C_{18}H_{19}O_3N_3S_2$ requires C, 55·6; H, 4·9; N, 10·8%).

(b) *From* cis-5-*phenyl*-2-*thiothiazolidine*-4-*carboxylic acid*. The acid (1 g.) was allowed to react with chloroacetic acid (2 g.) under essentially the same conditions as the *trans*-isomer. The product, m. p. 218° (decomp.), recrystallised from aqueous acetic acid as prismatic needles, m. p. 225—226° (decomp.) (Found: C, 53·9; H, 4·5; N, 6·1%).

Methyl cis-2-*oxo*-5-*phenylthiazolidine*-4-*carboxylate* was obtained as needles, m. p. 162—163°, from ethyl acetate–light petroleum when the acid prepared by either of the above described methods was esterified with diazomethane in ethyl acetate. The samples did not depress each other's m. p. (Found: C, 55·5; H, 4·7; N, 5·4%).

Hydrolysis of Methyl cis-2-*Oxo*-5-*phenylthiazolidine*-4-*carboxylate*.—(a) *With acid*. When the ester (0·4 g.) was heated under reflux with concentrated hydrochloric acid (2·5 ml.) and water (3·0 ml.) for 30 min. the *cis*-acid (0·35 g.) was obtained as needles, m. p. 220—222° (decomp.).

(b) *With alkali*. The ester (0·25 g.) in methyl alcohol (2 ml.) was hydrolysed with N-sodium hydroxide (2 ml.) at room temperature overnight. After acidification with N-hydrochloric acid (2 ml.) and concentration *trans*-2-oxo-5-phenylthiazolidine-4-carboxylic acid separated as needles, m. p. and mixed m. p. 190—192° (decomp.).

cis-2-*Oxo*-5-*phenylthiazolidine*-4-*carboxyamide*.—A mixture of *cis*-5-phenyl-2-thiothiazolidine-4-carboxyamide (5·0 g.), chloroacetic acid (10·0 g.), and water (50 ml.) was heated under reflux for 4 hr. cis-2-*Oxo*-5-*phenylthiazolidine*-4-*carboxyamide* (2·75 g.) was obtained as prisms, m. p. 210—212° (decomp.), raised to 219—221° (decomp.) on recrystallisation from aqueous acetic acid (Found: C, 53·6; H, 4·5; N, 12·6. $C_{10}H_{10}O_2N_2S$ requires C, 54·1; H, 4·6; N, 12·6%). The product depressed the m. p. of the corresponding *cis*-acid.

trans-2-*Oxo*-5-*phenylthiazolidine*-4-*carboxyamide*.—(a) *From methyl* trans-2-*oxo*-5-*phenylthiazolidine*-4-*carboxylate*. The required amide (0·65 g.), m. p. 192—193°, slowly separated when a mixture of the ester (1 g.), ammonia (*d* 0·88; 10 ml.), and methanol (5 ml.) was warmed on a steam-bath.

(b) *From* trans-2-*oxo*-5-*phenylthiazolidine*-4-*carboxylic acid*. The acid (1·0 g.) was heated under reflux with thionyl chloride (2 ml.) in chloroform (5 ml.) until dissolution was complete. The mixture was then concentrated *in vacuo* and the residue treated with ammonia (*d* 0·88; 5 ml.). The amide (0·9 g.) which separated was obtained as needles (from aqueous methanol), m. p. and mixed m. p. 192—193° (Found: C, 54·6; H, 4·4; N, 12·6%).

Reaction of 4-*Benzylidene*-2-*methylthiothiazol*-5-*one with Sodium Hydroxide*.—The thiazolone (1·0 g.) was heated under reflux for 2 hr. in N-sodium hydroxide (5 ml.) and alcohol (4 ml.). A little solid gradually separated and there was an odour of methanethiol. After the solution had been cooled, water (30 ml.) was added and the whole extracted with ether. The aqueous layer was then acidified with dilute hydrochloric acid and extracted with chloroform. After being washed and dried the extract was concentrated under reduced pressure to small volume and treated with light petroleum, a solid (0·35 g.), m. p. 156—160°, separating. This was dissolved in sodium hydrogen carbonate solution and treated with *S*-benzylthiuronium bromide to give the S-*benzylthiuronium salt* of *trans*-5-phenyl-2-thiothiazolidine-4-carboxylic acid, needles (from aqueous alcohol), m. p. 152—153°, alone and when mixed with a specimen prepared from the authentic acid [1] (Found: C, 53·5; H, 4·8; N, 10·3. $C_{18}H_{19}O_2N_3S_3$ requires C, 53·3; H, 4·7; N, 10·4%).

Reaction of trans-2-*Methylthio*-5-*phenylthiazoline*-4-*carboxylic Acid with Alkali*.—The acid (10 g.) was heated under reflux for 5 hr. in N-sodium hydroxide (110 ml.). An odour of thiol and ammonia became apparent. The resulting yellow solution was acidified hot with concentrated hydrochloric acid, a white solid (7·0 g.), m. p. 170—175° (decomp.), separating. This was removed and dissolved in aqueous sodium hydrogen carbonate and the solution filtered, then heated and acidified, to yield crude 5-*phenylthiazole*-4-*carboxylic acid* (6·0 g.), m. p. 182—183° (decomp.), raised to 193—194° (decomp.) on recrystallisation (needles) from alcohol (Found: C, 58·7; H, 3·6; N, 6·5; S, 15·4. $C_{10}H_7O_2NS$ requires C, 58·6; H, 3·4; N, 6·8; S, 15·6%).

Concentrating the original acid filtrate to about 50 ml. under reduced pressure gave a solid (0·9 g.), m. p. 127—142° (decomp.), which on recrystallisation from water yielded phenylpyruvic acid as prisms, m. p. 142—145° (decomp.) (Found: C, 65·7; H, 5·1. Calc. for $C_9H_8O_3$: C, 65·9; H, 4·9%).

Methyl 5-*phenylthiazole*-4-*carboxylate* was obtained from the acid by use of diazomethane or methyl alcohol containing a trace of sulphuric acid, as needles (from aqueous methanol), m. p. 100—101° (Found: C, 60·2; H, 4·1; N, 6·1; S, 14·6. $C_{11}H_9O_2NS$ requires C, 60·3; H, 4·1; N, 6·4; S, 14·6%).

XUM

5-Phenylthiazole-4-carboxyhydrazide was obtained by heating the above methyl ester with hydrazine hydrate in methanol, as needles (from methanol), m. p. 183—184° (Found: C, 55·0; H, 4·5; N, 19·1. $C_{10}H_9ON_3S$ requires C, 54·8; H, 4·1; N, 19·2%).

Action of Hydrogen Peroxide on trans-*5-Phenyl-2-thiothiazolidine-4-carboxylic Acid.*—A solution of the acid (2·0 g.) in 10% sodium hydroxide solution (10 ml.) was treated portionwise with hydrogen peroxide (3 ml.; 30-volume), the mixture being kept at room temperature by cooling. The resulting pale yellow solution, on acidification, yielded a white solid (1·2 g.) which recrystallised from aqueous ethanol as platelets, m. p. 190—192° (decomp.) after softening from 180°. Although it caused a slight depression in the m. p. of *trans*-2-oxo-5-phenylthiazolidine-4-carboxylic acid it gave correct analyses for this compound (cf. Kashida and Yamanaka [8]) (Found: C, 54·4; H, 4·2; N, 6·3%).

When the acid (4·0 g.) in 10% sodium hydroxide solution (20 ml.) was treated portionwise with hydrogen peroxide (8 ml.; 100-volume) without cooling, the product (2·7 g.) obtained on acidification next day had m. p. 164—166° (decomp.) which was not raised on recrystallisation from aqueous ethanol. When a solution of it (0·5 g.) in a little methanol was diluted with water, however, a white solid (0·25 g.) was obtained, having m. p. 170—178° (decomp.), which on recrystallisation from aqueous methanol gave colourless needles (0·15 g.), m. p. 191—192° (decomp.). This depressed the m. p. of *trans*-2-oxo-5-phenylthiazolidine-4-carboxylic acid to 160—166° (decomp.) but did not depress the m. p. of 5-phenylthiazole-4-carboxylic acid. From the mother-liquors there was obtained a solid (0·2 g.), m. p. 162—178° (decomp.), which after recrystallisation from aqueous methanol yielded colourless needles, m. p. 188—191° (decomp.) undepressed on admixture with *trans*-2-oxo-5-phenylthiazolidine-4-carboxylic acid. It depressed the m. p. of the thiazole acid.

When a mixture of the two acids (0·3 g. of each) was crystallised from aqueous ethanol, needles, m. p. 163—166° (decomp.), were obtained.

Action of Potassium Permanganate on trans-*5-Phenyl-2-thiothiazolidine-4-carboxylic Acid.*—A solution of the acid (2·5 g.) in water (15 ml.) containing sodium hydroxide (1·5 g.) was treated portionwise with potassium permanganate (4·5 g.) at 30°. After 1 hr. the mixture was filtered through kieselguhr, and the filtrate brought to pH 4 with concentrated hydrochloric acid, affording 5-phenylthiazole-4-carboxylic acid (1·8 g.), m. p. 185—187° (decomp.) raised to 191—192° (decomp.) on recrystallisation from aqueous acetic acid (Found: C, 58·3; H, 3·4; N, 6·4%).

BEECHAM RESEARCH LABORATORIES LIMITED,
BROCKHAM PARK, BETCHWORTH, SURREY.

[*Received, July 7th*, 1958.]

---

929. *Thiazolidines. Part V.*[1] *Synthesis of β-Alkylcysteines.*

By F. P. DOYLE, D. O. HOLLAND, P. MAMALIS, and A. NORMAN.

Synthesis of β-methyl-, β-*iso*propyl-, and ββ-dimethyl-cysteine from the appropriate 4-alkylidene-2-thiothiazolid-5-ones is described. Correlation of the β-methylcysteine (thiothreonine) produced by this route with the A-isomer prepared by Carter *et al.*[2] and also with threonine is suggested.

SYNTHESIS of β-alkylcysteines from 2-alkyl-4-alkylidene- or 4-alkylidene-2-aryl-oxazolones has been often described [3] but little attention has been paid to the route [4] from 4-alkylidene-2-thiothiazolid-5-ones (I). In view of the ready availability of the starting material, 2-thiothiazolid-5-one,[5] we concentrated our attention on this route.

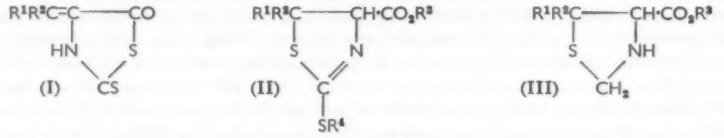
4-Ethylidene-2-thiothiazolid-5-one (I; $R^1 = Me$, $R^2 = H$) was converted into 5-methyl-2-thiothiazolidine-4-carboxylic acid (II; $R^1 = Me$, $R^2 = R^3 = R^4 = H$) * by methanolic

* See footnote on p. 4584.

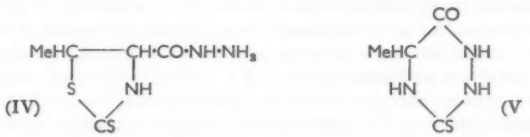
[1] Parts I—IV, preceding papers.
[2] Carter, Stevens, and Ney, *J. Biol. Chem.*, 1941, **139**, 247.
[3] (*a*) "Chemistry of Penicillin," Princeton Univ. Press, Princeton, 1949, pp. 465 *et seq.*; (*b*) Savard, Richardson, and Grant, *Canad. J. Res.*, 1946, **24**, *B*, 28; Neher, Spillmann, Werner, Wettstein, and Miescher, *Helv. Chim. Acta*, 1946, **29**, 1874; Tatsuoka, Miyamoto, Shiu, and Tamura, *J. Penicillin, Japan*, 1947, **1**, 382; Tatsuoko, Ueno, and Kinoshita, *J. Pharm. Soc. Japan*, 1949, **69**, 291.
[4] Cook, Hunter, and Pollock, *J.*, 1950, 1892.
[5] Cook, Heilbron, and Levy, *J.*, 1948, 201; Holland, B.P. 689,243/1951, 733,090/1953.

XUM

potassium hydroxide. The acid was characterised as its methyl ester (II; $R^1 = R^3 = Me$, $R^2 = R^4 = H$) which with hydrazine readily gave the hydrazide (IV) and not the triazine (V) which might have been expected from the analogous experiment in the 5-phenyl



series.[1] The acid with methyl iodide and potassium carbonate in acetone gave the *S*-methyl derivative (II; $R^1 = R^4 = Me$, $R^2 = R^3 = H$) as an oil (characterised as the *S*-benzylthiuronium salt), which with diazomethane gave its methyl ester (II; $R^1 = R^3 = R^4 = Me$, $R^2 = H$), and this with aluminium amalgam gave methyl 5-methylthiazolidine-4-carboxylate (III; $R^1 = R^3 = Me$, $R^2 = H$) as an oil characterised as the hydrazide.



The last-mentioned ester, when heated with methanolic mercuric chloride, gave methyl α-amino-β-mercaptopropionate hydrochloride (VI; $R^1 = R^3 = Me$, $R^2 = H$) by ring-fission and elimination of formaldehyde. Acid-hydrolysis of this ester gave α-amino-β-mercaptopropionic acid (β-methylcysteine, thiothreonine) hydrochloride (VI; $R^1 = Me$, $R^2 = R^3 = H$) also obtained directly, in the same isomeric form, by heating 5-methyl-2-thiothiazolidine-4-carboxylic acid (II; $R^1 = Me$, $R^2 = R^3 = R^4 = H$) with concentrated hydrochloric acid in a sealed tube.

Carter *et al.*[2] found that both diastereoisomeric forms of α-amino-β-mercaptopropionic acid (designated A and B) were formed when 4-ethylidene-2-phenyl-5-oxazolone [6] reacted with toluene-ω-thiol under alkaline conditions and the resulting *N*-benzoyl-*S*-benzyl derivatives (VII; $R^3 = H$, $R^1 = CH_2Ph$, $R^2 = Bz$) were hydrolysed and debenzylated. It was of interest to determine which of these two forms corresponded to the single form described in the above series of reactions, and also to correlate the isomers with the threonine or *allo*threonine structure (VIII; $R^1 = R^2 = H$).

Our ester (VI; $R^1 = R^3 = Me$, $R^2 = H$) with benzyl bromide and triethylamine gave an oily *S*-benzyl derivative (VII; $R^3 = Me$, $R^1 = CH_2Ph$, $R^2 = H$), whose hydrochloride, m. p. 131—132°, appeared to be identical (m. p. and mixed m. p.) with methyl α-amino-β-benzylthiopropionate hydrochloride prepared by the action of methanolic hydrogen chloride on the *S*-benzylthiothreonine A of Carter *et al.*[2] The corresponding *S*-benzylthiothreonine B[2] gave a methyl ester hydrochloride, m. p. 171°, under the same conditions. Benzoylation of the *S*-benzyl ester hydrochloride, m. p. 131—132°, followed by hydrolysis with hydrochloric acid, gave a compound (VII; $R^1 = CH_2Ph$, $R^2 = Bz$, $R^3 = H$) identical (mixed m. p.) with *N*-benzoyl-*S*-benzylthiothreonine A [it was shown that benzoylation (Schotten–Baumann) did not cause inversion of either the A or the B form of *S*-benzylthiothreonine methyl ester]. As an alternative route to the same *N*-benzoyl-*S*-benzylthiothreonine, our ester (VI; $R^1 = R^3 = Me$, $R^2 = H$) was benzoylated under the same conditions to give the neutral methyl α-benzamido-β-benzoylthiopropionate as well as the expected alkali-soluble mono-*N*-benzoyl derivative (VII; $R^1 = H$, $R^2 = Bz$, $R^3 = Me$). The latter product, on cold alkaline hydrolysis followed by reaction with benzyl chloride and alkali, gave an *N*-benzoyl-*S*-benzylthiothreonine again identical with Carter's A derivative.

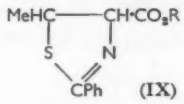
[6] Finar and Libman, *J.*, 1949, 2726.

By analogy with the work of Sicher *et al.*,[19] and with that reported in previous papers in this series,[1] it is considered likely that the stable form of 5-methyl-2-thiothiazolidine-4-carboxylic acid used in the above reaction has the *trans*-configuration and that subsequent

(VI) $R^1R^2C(SH)\cdot CH(NH_2)\cdot CO_2R^3$

(VII) $Me\cdot CH(SR^1)\cdot CH(NHR^2)\cdot CO_2R^3$

(VIII) $Me\cdot CH(OH)\cdot CH(NHR^1)\cdot CO_2R^2$



(IX)

reactions are unlikely to have affected the configuration of the derivatives. Since the thiothreonine prepared appears to be identical with the A isomer of Carter *et al.*, this implies that this isomer has the *threo*-configuration. Support for this was obtained when the hydrochloride of *allo*threonine methyl ester (VIII; $R^1 = H$, $R^2 = Me$) with thiobenzoylthioacetic acid in the presence of pyridine gave the thiobenzoyl derivative [9] (VIII; $R^1 =$ CSPh, $R^2 = Me$). This was cyclised with cold thionyl chloride to give methyl 5-methyl-2-phenylthiazoline-4-carboxylate (IX; R = Me). By analogy with the observations of Fry [9] and of Attenburrow *et al.*,[10] it was assumed that the *trans*-form of the thiazoline (corresponding to the threonine configuration) was produced in this reaction, inversion occurring during the replacement of the β-hydroxy-group of *allo*threonine by the sulphur of the thiobenzoyl group. Hydrolysis of the ester (IX; R = Me) with hot hydrochloric acid gave a mercapto-amino-acid, m. p. 184—186° (decomp.), which was benzylated in liquid ammonia to give an *S*-benzyl(thiothreonine), m. p. 171—173°, from which was obtained an *N*-benzoyl derivative, m. p. 140—142° not depressed on admixture with Carter's A compound.

These findings are contrary to those reported recently, and some time after this work had been completed, by Arnstein [11] who suggests that it is Carter's B isomer which is identical with the thiothreonine prepared from *allo*threonine (and incidentally also from threonine) by the same route as ours.

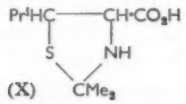
4-*iso*Butylidene-2-thiothiazolid-5-one [12] (I; $R^1 = Pr^i$, $R^2 = H$) with methanolic potassium hydroxide gave the expected *trans*-5-*iso*propyl-2-thiothiazolidine-4-carboxylic acid (II; $R^1 = Pr^i$, $R^2 = R^3 = R^4 = H$). *S*-Methylation with methyl iodide in aqueous sodium hydroxide, followed by esterification and reduction as described previously, gave the thiazolidine ester (III; $R^1 = Pr^i$, $R^2 = H$, $R^3 = Me$). Ring-fission as before gave methyl α-amino-β-mercapto*iso*hexanoate (VI; $R^1 = Pr^i$, $R^2 = H$, $R^3 = Me$) as the hydrochloride which was hydrolysed by hydrochloric acid to *threo*-α-amino-β-mercapto*iso*hexanoic acid (β-*iso*propylcysteine) hydrochloride [3] (VI; $R^1 = Pr^i$, $R^2 = R^3 = H$). This product exhibited the usual colour reactions of the thiol group and readily gave an *iso*propylidene derivative (X) when warmed with acetone. As was observed with β-methylcysteine methyl ester, benzoylation of β-*iso*propylcysteine methyl ester under Schotten–Baumann conditions gave a neutral product, which was assumed to be the *NS*-dibenzoyl derivative, even with only one equivalent of benzoyl chloride.

In parallel experiments 5-*iso*propyl-2-thiothiazolidine-4-carboxylic acid (II; $R^1 = Pr^i$, $R^2 = R^3 = R^4 = H$) gave an oily methyl ester which was smoothly converted with aqueous ammonia into the amide (XI; R = H) identical with the material isolated from the reaction of 4-*iso*butylidene-2-thiothiazolid-5-one (I; $R^1 = Pr^i$, $R^2 = H$) with aqueous ammonia.[4,13] With methyl iodide and alkali the amide gave *trans*-2-methylthio-5-*iso*propylthiazolidine-4-carboxyamide (XI; R = Me) which, as in the case of the corresponding ester (II; $R^1 = Pr^i$, $R^2 = H$, $R^3 = R^4 = Me$), was reduced with aluminium amalgam to the thiazolidine amide (XII; R = H) also obtained directly from the ester (III; $R^1 = Pr^i$, $R^2 = H$,

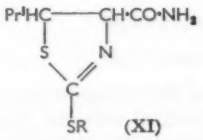
[7] Sicher, Svoboda, and Farkas, *Coll. Czech. Chem. Comm.*, 1955, **20**, 1439.
[8] Cf. Crawhall and Elliott, *J.*, 1951, 2071.
[9] Fry, *J. Org. Chem.*, 1949, **14**, 887.
[10] Attenburrow, Elliott, and Penny, *J.*, 1948, 310.
[11] Arnstein, *Biochem. J.*, 1958, **68**, 333.
[12] Billimoria and Cook, *J.*, 1949, 2323.
[13] Doyle, Holland, and Nayler, *J.*, 1955, 2265.

XUM

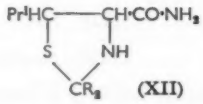
R^3 = Me). Ring-fission of the amide with mercuric chloride in methanol proceeded normally, to give *threo*-α-amino-β-mercapto*iso*hexanamide (β-*iso*propylcysteine amide) hydrochloride which, like the corresponding acid hydrochloride, gave the *iso*propylidene derivative (XII; R = Me).



(X)



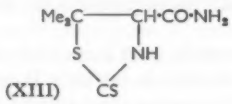
(XI)



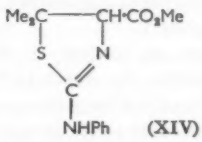
(XII)

2-Methylthio-5-*iso*propylthiazoline-4-carboxylic acid (II; R^1 = Pr^i, R^2 = R^3 = H, R^4 = Me), like the two forms of the 5-phenyl compound,[1] on successive treatment with thionyl chloride and ammonia gave a compound isomeric with the amide (XI; R = Me) described above. By analogy with the suggestion in Part III,[1] this isomer is believed to be 4-methyl-2-(methylthio-thiocarbonylamino)pent-2-enamide. An anilide prepared similarly is believed to have an analogous structure.

Unlike the two β-alkylcysteines described above, α-amino-β-mercapto*iso*valeric acid (VI; R^1 = R^2 = Me, R^3 = H) (penicillamine) exists in only one optically inactive form. An attempt to prepare this compound by the reduction of 5 : 5-dimethyl-2-thiothiazolidine-4-carboxylic acid (II; R^1 = R^2 = Me, R^3 = R^4 = H) with aluminium and hydrochloric



(XIII)



(XIV)

acid [14] was unsuccessful in our hands. The required thiothiazolidine (II; R^1 = R^2 = Me, R^3 = R^4 = H) was readily obtained from 4-*iso*propylidene-2-thiothiazolid-5-one (I; R^1 = R^2 = Me) by reaction with methanolic potassium hydroxide.[15] The non-acidic gummy by-product noted by Chatterjee *et al.* has now been shown to be the methyl ester (II; R^1 = R^2 = R^3 = Me, R^4 = H) identical with a sample prepared from penicillamine methyl ester and carbon disulphide.[16] It was readily converted into the amide (XIII) by aqueous ammonia.

In view of our failure to reduce the thiazoline (II; R^1 = R^2 = Me, R^3 = R^4 = H) directly to penicillamine it was converted into the *S*-methyl derivative and its methyl ester as described earlier. The same ester was also obtained as an oil when methyl 5 : 5-dimethyl-2-thiothiazolidine-4-carboxylate [17] (II; R^1 = R^2 = R^3 = Me, R^4 = H) was allowed to react with diazomethane. It was identified as a picrate identical with that derived from an authentic specimen and gave the 2-anilino-compound (XIV) with warm aniline.

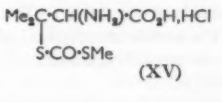
Reduction of the ester (II; R^1 = R^2 = R^3 = R^4 = Me) with aluminium amalgam gave the crystalline methyl 5 : 5-dimethylthiazolidine-4-carboxylate (III; R^1 = R^2 = R^3 = Me), m. p. 43—44°. Neher *et al.*[3b] describe this ester, prepared from the corresponding acid and diazomethane, as having m. p. 204—207° (decomp.). Its ring-fission with mercuric chloride, followed by acid-hydrolysis of the penicillamine ester, gave crude penicillamine (VI; R^1 = R^2 = Me, R^3 = H) as its hydrochloride characterised by conversion into its *iso*propylidene derivative.

With hot hydrochloric acid 5 : 5-dimethyl-2-methylthiothiazoline-4-carboxylic acid

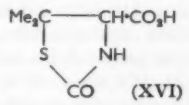
[14] Ref. 3*a*, p. 467.
[15] Cf. Chatterjee, Cook, Heilbron, and Levy, *J.*, 1948, 1337.
[16] Cook, Elvidge, and Shaw, *J.*, 1949, 2367.
[17] Süs, *Annalen*, 1948, **561**, 31.

XUM

(II; $R^1 = R^2 = R^4 = Me$, $R^3 = H$) gave *S*-(methylthio-carbonyl)penicillamine hydrochloride (XV). On treatment with aqueous sodium hydroxide, the latter compound readily lost methanethiol, to give 5 : 5-dimethyl-2-oxothiazolidine-4-carboxylic acid (XVI) identical with the product obtained from the thiazoline ester (II; $R^1 = R^2 = R^3 = Me$, $R^4 = H$) and alkaline hydrogen peroxide.[16] The same compound was prepared in improved



(XV)



(XVI)

yield by treating the thiothiazolidine acid (II; $R^1 = R^2 = Me$, $R^3 = R^4 = H$) with aqueous chloroacetic acid. Crawhall and Elliott [8] found that 2-oxothiazolidine-4-carboxylic acid itself was cleaved to cysteine by hot hydrochloric acid, but we have found that the 5 : 5-dimethyl derivative, like the 5-phenyl compound,[1] resists such treatment.

Experimental

4-Alkylidene-2-thiothiazolid-5-ones.—4-Ethylidene-, 4-*iso*butylidene-, and 4-*iso*propylidene-2-thiothiazolid-5-ones were prepared as described by Billimoria and Cook.[12]

Reaction of 4-Alkylidene-2-thiothiazolid-5-ones with Potassium Hydroxide.[15]—The thiazolidone (0·1 mole) was added to a warm solution of potassium hydroxide (14·0 g.) in methanol (250 ml.) and left for 24 hr. at room temperature. The solution, after filtration, was evaporated *in vacuo* to a syrup which was dissolved in water (100 ml.) and acidified with hydrochloric acid. The resulting precipitate was collected and extracted with excess of aqueous sodium hydrogen carbonate solution, and the filtered extracts were acidified to give the 5-alkyl-2-thiothiazolidine-4-carboxylic acids shown in the Table.

5-Substituted 2-thiothiazolidine-4-carboxylic acids (II; $R^3 = R^4 = H$).

		Yield			Found (%)			Required (%)		
R^1	R^2	(%)	M. p.	Formula	C	H	N	C	H	N
Me	H	76	182—183° [a]	$C_5H_7O_2NS_2$	34·1	4·0	7·9	34·1	3·8	8·1
Pr^i	H	72	168—170 [b]	$C_7H_{11}O_2NS_2$	41·3	5·8	6·8	41·0	5·4	6·3
Me	Me	76	148 [c]	$C_6H_9O_2NS_2$	38·3	4·7	7·0	37·7	4·8	7·3

[a] Prisms from ethyl acetate–light petroleum. [b] Needles from water. [c] Needles from chloroform–light petroleum; Chatterjee *et al.*[14] give m. p. 145°.

Methyl 5-Methyl-2-thiothiazolidine-4-carboxylate.—5-Methyl 2-thiothiazolidine-4-carboxylic acid (5·0 g.), methanol (50 ml.), and concentrated sulphuric acid (6 drops) were refluxed together for 3 hr. The solution was concentrated and the residue stirred with aqueous methanol to give the *methyl ester* (4·7 g.) which recrystallised from aqueous methanol and then from ethyl acetate–light petroleum, to give prisms, m. p. 85—87° (Found: C, 37·2; H, 4·9; N, 7·5. $C_6H_9O_2NS_2$ requires C, 37·7; H, 4·8; N, 7·3%).

5-Methyl-2-thiothiazolidine-4-carboxyhydrazide.—The above methyl ester (1·0 g.) was left with methanol (10·0 ml.) and 90% hydrazine hydrate (0·4 ml.) for 24 hr. Concentration and addition of water gave the hydrazide which separated from aqueous methanol as prisms (0·6 g.), m. p. 172° (decomp.) (Found: C, 31·7; H, 4·8; N, 22·5. $C_5H_9ON_3S_2$ requires C, 31·4; H, 4·8; N, 22·0%).

5-isoPropyl-2-thiothiazolidine-4-carboxyamide.—5-*iso*Propyl-2-thiothiazolidine-4-carboxylic acid (10 g.), methanol (100 ml.), and sulphuric acid (0·5 ml.) were refluxed for 3 hr., then evaporated to small volume. The residue was dissolved in chloroform, washed with sodium hydrogen carbonate solution, dried, and recovered as an amber oil. This ester (2 g.) and ammonium hydroxide (15 ml.; *d* 0·88) were mixed and methanol was added until a one-phase solution was present. After 24 hr. this was evaporated to leave the *amide* (1·8 g.) which crystallised from aqueous methanol as needles, m. p. 152—153°, identical (mixed m. p.) with a sample prepared by the reaction of 4-*iso*butylidene-2-thiothiazolid-5-one with ammonia [4, 13] (Found: C, 41·3; H, 5·0; N, 13·9. Calc. for $C_7H_{12}ON_2S_2$: C, 41·2; H, 6·0; N, 13·7%).

Methyl 5 : 5-Dimethyl-2-thiothiazolidine-4-carboxylate.—The residue insoluble in sodium

hydrogen carbonate from the reaction of 4-*iso*propylidene-2-thiothiazolid-5-one with potassium hydroxide crystallised from aqueous methanol, to give methyl 2-thio-5 : 5-dimethylthiazolidine-4-carboxylate, m. p. 106—107°, identical with a sample prepared by Cook, Elvidge, and Shaw's method [16] (Found: C, 41·1; H, 5·8; N, 6·8. Calc. for $C_7H_{11}O_2NS_2$: C, 41·0; H, 5·4; N, 6·8%).

5 : 5-*Dimethyl*-2-*thiothiazolidine*-3-*carboxyamide*.—The preceding methyl ester (1·0 g.) was left in aqueous ammonia (10 ml.; *d* 0·88) at room temperature for 24 hr. Evaporation gave a buff solid (0·5 g.) which crystallised from water to give the amide as needles, m. p. 175—177°, identical with a sample prepared by the method of Doyle *et al.*[13] (Found: C, 37·9; H, 5·4; N, 15·1. Calc. for $C_6H_{10}ON_2S_2$: C, 37·8; H, 5·3; H, 14·7%).

5-*Methyl*-2-*methylthiothiazoline*-4-*carboxylic Acid*.—5-Methyl-2-thiothiazolidine-4-carboxylic acid (5·0 g.), acetone (100 ml.), and potassium carbonate (10 g.) were refluxed with methyl iodide (20 ml.) for 2 hr. The solid was separated and the filtrate concentrated to yield the *S*-methyl-acid as an oil (5·0 g.). The S-*benzylthiuronium salt* formed needles (from dioxan), m. p. 149—150° (Found: C, 46·9; H, 5·7; N, 11·7. $C_{14}H_{19}O_2N_3S_3$ requires C, 47·0; H, 5·4; N, 11·8%).

2-*Methylthio*-5-iso*propylthiazoline*-4-*carboxylic Acid*.—5-*iso*Propyl-2-thiothiazolidine-4-carboxylic acid (8·7 g.) in aqueous N-sodium hydroxide (100 ml.) was stirred with methyl iodide (4 ml.) for 24 hr. at room temperature. The solution, after concentration, was acidified with concentrated hydrochloric acid, and the oil extracted with chloroform. Evaporation of the dried extract and recrystallisation of the residue (4·2 g.) from chloroform–light petroleum gave the *acid* as prisms, m. p. 74—75° (Found: C, 43·7; H, 6·5; N, 6·9. $C_8H_{13}O_2NS_2$ requires C, 43·7; H, 6·0; N, 6·4%) [S-*benzylthiuronium salt*, m. p. 148—149°, needles from aqueous alcohol (Found: C, 49·6; H, 5·8; N, 11·1; S, 25·2. $C_{16}H_{23}O_2N_3S_3$ requires C, 49·7; H, 6·0; N, 11·3; S, 24·9%)].

2-*Methylthio*-5-iso*propylthiazoline*-4-*carboxyamide*.—This was prepared similarly from 5-*iso*propyl-2-thiothiazolidine-4-carboxyamide (1 g.) and methyl iodide (0·5 ml.) in N-sodium hydroxide (5·5 ml.). The *methylthio-amide* crystallised from aqueous methanol as needles, m. p. 127—128° (Found: C, 44·1; H, 7·0; N, 13·2. $C_8H_{14}ON_2S_2$ requires C, 44·0; H, 6·5; N, 12·8%).

Reaction of 2-*Methylthio*-5-iso*propylthiazoline*-4-*carboxylic Acid with Thionyl Chloride*.—The acid hydrochloride (3·0 g.), thionyl chloride (5 ml.), and dry chloroform (15 ml.) were refluxed for 0·75 hr. to give a clear solution which was left for 24 hr., then evaporated to a syrup. After double evaporation with dry benzene the presumed " acid chloride " tended to crystallise. It was dissolved in dry benzene (15 ml.) and this solution (7·5 ml.) was shaken with aqueous ammonia (4 ml.; *d* 0·88) for 24 hr. The resulting solution was diluted with chloroform and acidified with dilute hydrochloric acid, and the organic layer separated. This was washed with dilute sodium hydrogen carbonate solution and water, and then dried ($MgSO_4$). Concentration and addition of light petroleum gave 4-*methyl*-2-(*methylthio-thiocarbonylamino*)*pent*-2-*enamide* as cream-coloured needles, m. p. 90—91° (from light petroleum) (Found: C, 44·8; H, 6·1; N, 12·5. $C_8H_{14}ON_2S_2$ requires C, 44·1; H, 6·5; N, 12·8%).

The " acid chloride " (7·5 ml. of the solution in benzene) and aniline (3 ml.) were left for 24 hr., diluted with chloroform, and washed with dilute hydrochloric acid, dilute sodium hydrogen carbonate solution, and water. The organic extracts were dried and concentrated with light petroleum to give the analogous *anilide* as needles, m. p. 97—98° (Found: C, 57·4; H, 5·8; N, 9·6. $C_{14}H_{18}ON_2S_2$ requires C, 57·2; H, 6·2; N, 9·5%).

5 : 5-*Dimethyl*-2-*methylthiothiazoline*-4-*carboxylic Acid*.—This *acid* was prepared from 5 : 5-dimethyl-2-thiothiazolidine-4-carboxylic acid (12 g.) and methyl iodide (6 ml.) in N-sodium hydroxide (120 ml.) as prisms (9·1 g.), m. p. 126° (from ethyl acetate) (Found: C, 40·6; H, 5·0; N, 6·8. $C_7H_{11}O_2NS_2$ requires C, 40·8; H, 5·4; N, 6·8%). The *sodium salt* was only moderately water-soluble and was isolated directly from the reaction mixture. It crystallised from ethanol as needles, m. p. >280° (Found: C, 36·6; H, 4·4; N, 6·7. $C_7H_{10}O_2NS_2Na$ requires C, 37·0; H, 4·3; N, 6·2%).

Methyl 5-*Methyl*-2-*methylthiothiazoline*-4-*carboxylate*.—An excess of ethereal diazomethane was added to crude 5-methyl-2-methylthiothiazoline-4-carboxylic acid (5·0 g.) in ether (100 ml.). After 24 hr. the ether was evaporated and the residue distilled to give the *methyl ester* (4·5 g.), b. p. 93—95°/0·3 mm., n_D^{18} 1·5485 (Found: C, 41·0; H, 5·8; N, 7·0. $C_7H_{11}O_2NS_2$ requires C, 41·0; H, 5·4; N, 6·8%).

Methyl 2-*Methylthio*-5-iso*propylthiazoline*-4-*carboxylate*.—This *ester* (15·0 g.), b. p. 118—

120°/1·5 mm., was prepared similarly from 2-methylthio-5-*iso*propylthiazoline-4-carboxylic acid (15·8 g.) (Found: C, 46·9; H, 6·9; N, 6·1; S, 27·7. $C_9H_{15}O_2NS_2$ requires C, 46·4; H, 6·5; N, 6·0; S, 27·5%).

Methyl 5 : 5-Dimethyl-2-methylthiothiazoline-4-carboxylate.—(1) This *ester*, prepared as above from 5 : 5-dimethyl-2-methylthiothiazoline-4-carboxylic acid (14 g.), had b. p. 82—83°/0·15 mm. (14·7 g.) (Found: C, 44·1; H, 5·3; N, 6·4. $C_8H_{13}O_2NS_2$ requires C, 43·8; H, 6·0; N, 6·4%). Its *picrate* formed needles, m. p. 107—108°, from aqueous ethanol (Found: C, 37·5; H, 3·9; N, 13·0. $C_{14}H_{16}O_9N_4S_2$ requires C, 37·4; H, 3·6; N, 12·5%). (2) Excess of ethereal diazomethane was added to a suspension of methyl 5 : 5-dimethyl-2-thiothiazolidine-4-carboxylate (0·5 g.) in ether (10 ml.). After 24 hr. evaporation gave the ester whose picrate had m. p. and mixed m. p. 107—108° (Found: C, 37·7; H, 3·6; N, 12·7%).

Methyl 2-Anilino-5 : 5-dimethylthiazoline-4-carboxylate.—Methyl 5 : 5-dimethyl-2-methylthiothiazoline-4-carboxylate (2·2 g.) and aniline (0·95 g.) were heated at 95° for 6 hr. and unchanged reactants were removed *in vacuo*. The residue, recrystallised from ethanol, gave the *anilino-derivative* (0·6 g.) as needles, m. p. 160—161° (Found: C, 59·6; H, 6·0; N, 10·6. $C_{13}H_{16}O_2N_2S$ requires C, 59·1; H, 6·1; N, 10·6%).

5-Methylthiazolidine-4-carboxylic Acid and its Derivatives.—Methyl 2-methylthiothiazoline-4-carboxylate (10·0 g.) in methanol (300 ml.) was added to amalgamated aluminium foil (7·0 g.). After 24 hr. the solids were extracted with hot methanol (3 × 300 ml.), the combined filtrates evaporated, and the residual oil distilled *in vacuo*, to give *methyl 5-methylthiazolidine-4-carboxylate* (4·4 g.), b. p. 66—67°/0·5 mm., n_D^{20} 1·5050 (Found: C, 44·7; H, 7·0; N, 9·0. $C_6H_{11}O_2NS$ requires C, 44·7; H, 6·9; N, 8·7%). Alcoholic hydrazine hydrate gave the *hydrazide*, m. p. 111—113° (Found: C, 37·2; H, 6·7; N, 26·3. $C_5H_{11}ON_3S$ requires C, 37·2; H, 6·8; N, 26·0%).

*Methyl 5-iso*Propylthiazolidine-4-carboxylate.*—This *ester* (4·8 g.) was prepared similarly from methyl 2-methylthio-5-*iso*propylthiazoline-4-carboxylate (10 g.) as a pale yellow oil, b. p. 67—68°/0·5 mm. (Found: C, 50·8; H, 8·0; N, 7·6. $C_8H_{15}O_2NS$ requires C, 51·0; H, 8·0; N, 7·4%) [*hydrochloride*, needles (from methanol–ether), m. p. 133—134° (Found: C, 42·7; H, 7·3; N, 6·5; Cl, 15·8. $C_8H_{16}O_2NSCl$ requires C, 42·7; H, 7·2; N, 6·2; Cl, 15·7%)].

*5-iso*Propylthiazolidine-4-carboxyamide.*—(1) 2-Methylthio-5-*iso*propylthiazoline-4-carboxyamide (20 g.) was similarly reduced to 5-*iso*propylthiazolidine-4-carboxyamide, needles (10 g.), 126—127° (from aqueous methanol) (Found: C, 48·3; H, 8·2; N, 16·2. $C_7H_{14}ON_2S$ requires C, 48·4; H, 8·1; N, 16·1%).

(2) Methyl 5-*iso*propylthiazolidine-4-carboxylate (0·45 g.), ammonia (5 ml.; *d* 0·88) and methanol (4 ml.) were left for 24 hr. at room temperature. Evaporation gave a solid amide (0·35 g.) which, crystallised from aqueous methanol, had m. p. and mixed m. p. 126°.

Methyl 5 : 5-Dimethylthiazolidine-4-carboxylate.—Methyl 5 : 5-dimethyl-2-methylthiothiazoline-4-carboxylate (21·5 g.) was similarly reduced to the *thiazolidine* (12·1 g.), b. p. 70—75°/0·2 mm., prisms, m. p. 43—44° (from light petroleum) (Found: C, 47·9; H, 7·2; N, 8·2. $C_7H_{13}O_2NS$ requires C, 47·9; H, 7·5; N, 8·0%).

β-Methylcysteine (Thiothreonine) Methyl Ester Hydrochloride.—Methyl 5-methylthiazolidine-4- carboxylate (2·0 g.) and 10% methanolic mercuric chloride (50 ml.) were heated under reflux for 2 hr. The cooled suspension of mercuric salts was treated with hydrogen sulphide for 1 hr., then filtered, and evaporated. The residue gave *thiothreonine methyl ester hydrochloride*, m. p. 138—139° (from propan-2-ol), giving an intense violet colour with sodium nitroprusside (Found: C, 32·5; H, 6·3; N, 7·4; S, 16·9. $C_5H_{12}O_2NSCl$ requires C, 32·4; H, 6·5; N, 7·5; S, 17·3%).

Thiothreonine Hydrochloride.—(1) The foregoing ester (1·0 g.) was refluxed with 5N-hydrochloric acid (15 ml.) for 2·5 hr. Evaporation and drying *in vacuo* over potassium hydroxide gave *thiothreonine hydrochloride* as needles, m. p. 184—185° (from methanol–ether) (Found: C, 28·2; H, 5·9; N, 8·5. $C_4H_{10}O_2NSCl$ requires C, 28·0; H, 5·9; N, 8·2%).

(2) 5-Methyl-2-thiothiazolidine-4-carboxylic acid (5·0 g.) and concentrated hydrochloric acid (40 ml.) were heated in a sealed tube at 110—120° for 60 hr., then evaporated, leaving thiothreonine hydrochloride (1·8 g.), needles, m. p. and mixed m. p. 184—185° (from methanol–ether).

S-Benzylthiothreonine Methyl Ester Hydrochloride.—Triethylamine (9·0 ml.) and then benzyl bromide (2·6 ml.) were added with shaking to thiothreonine methyl ester hydrochloride (3·7 g.) suspended in dry chloroform (15 ml.). After 1 hr. the mixture was concentrated, basified with 4N-sodium hydroxide, and extracted with ether. Evaporation of the extracts afforded an oil, converted by ethereal hydrogen chloride into crystalline *S-benzylthiothreonine methyl ester hydrochloride* (3·5 g.), m. p. 129—130°. Crystallisation from propan-2-ol gave

needles, m. p. 131—132° (Found: C, 51·8; H, 6·7; N, 5·1. $C_{12}H_{16}O_2NSCl$ requires C, 52·2; H, 6·6; N, 5·1%).

N-Benzoyl-S-benzylthiothreonine Methyl Ester.—*S*-Benzylthiothreonine methyl ester hydrochloride (1·4 g.) was shaken with N-sodium hydroxide (10·0 ml.) and benzoyl chloride (0·58 ml.) for 20 min. The insoluble product (1·65 g.) gave *N-benzoyl-S-benzylthiothreonine methyl ester* as needles, m. p. 88—89°, from ethyl acetate–light petroleum (Found: C, 66·7; H, 6·5; N, 4·4. $C_{19}H_{21}O_3NS$ requires C, 66·6; H, 6·2; N, 4·1%).

Benzoylation of Thiothreonine Methyl Ester Hydrochloride.—The ester hydrochloride (1·9 g.) was shaken with N-sodium hydroxide (32 ml.) and benzoyl chloride (2·0 ml.) for 5 min. The oil which separated was extracted with ether, and the extracts were evaporated. Crystallisation of the residue from ether–light petroleum (b. p. 40—60°) gave NS-*dibenzoylthiothreonine methyl ester* (1·45 g.), m. p. 89—90° (Found: C, 63·9; H, 5·4; N, 3·9; S, 9·4. $C_{19}H_{19}O_4NS$ requires C, 63·9; H, 5·4; N, 3·9; S, 9·0%). The aqueous layer was acidified and extracted with chloroform, to give *N-benzoylthiothreonine methyl ester* a sneedles, m. p. 84—85° (from ether–light petroleum) (Found: C, 56·8; H, 5·9; N, 5·3. $C_{12}H_{15}O_3NS$ requires C, 57·0; H, 6·0; N, 5·5%).

The *N*-benzoyl ester (1 g.) was left in N-sodium hydroxide (10 ml.) overnight. Acidification gave *N-benzoylthiothreonine* as needles (from aqueous alcohol), m. p. 149—150° (Found: C, 54·9; H, 5·3; N, 6·3. $C_{11}H_{13}O_3NS$ requires C, 55·3; H, 5·5; N, 5·9%).

N-Benzoyl-S-benzyl(thiothreonine).—(1) *N*-Benzoyl-*S*-benzylthiothreonine methyl ester (1·5 g.) was heated with concentrated hydrochloric acid (7·5 ml.), water (15 ml.), and acetic acid (25 ml.) for 30 min. under reflux. Water (5 ml.) was added and after 24 hr. the product was collected (1·05 g.); m. p. 142—144°. *N*-Benzoyl-*S*-benzylthiothreonine separated from benzene as plates, m. p. 142—143°, not depressed on admixture with a specimen prepared according to Carter *et al.*[1] (see below) (Found: C, 65·5; H, 6·0; N, 4·5. Calc. for $C_{18}H_{19}O_3NS$: C, 65·6; H, 5·8; N, 4·2%). The phenethylamine salt formed needles, m. p. and mixed m. p. 165—167° from ethyl acetate–ethanol (Found: C, 68·9; H, 6·8; N, 6·0. Calc. for $C_{26}H_{30}O_3N_2S$: C, 69·3; H, 6·7; N, 6·2%).

(2) *N*-Benzoylthiothreonine (2·4 g.) was stirred with N-sodium hydroxide (23 ml.) and benzyl chloride (1·3 g.) for 2 hr. The mixture was extracted once with ether, and the aqueous layer acidified with hydrochloric acid, to give a solid which on crystallisation from benzene furnished *N*-benzoyl-*S*-benzylthiothreonine (2·5 g.), m. p. 140—143°, not depressed on admixture with an authentic specimen of the A-series (see below).

Benzoylation of S-Benzylthiothreonine A and B.—The method of Carter *et al.*[2] was used to prepare reference samples of *N*-benzoyl-*S*-benzylthiothreonine A, m. p. 142—143° (lit., m. p. 143—145°) and B, m. p. 183—185° (lit., m.p. 177—182°).

Esterification of S-Benzylthiothreonine A and B.—Dry hydrogen chloride was passed into a suspension of *S*-benzylthiothreonine A (11·5 g.) in dry methanol (160 ml.) for 1·5 hr. without external cooling. After 24 hr. the methanol was evaporated, to give the *methyl ester hydrochloride A* (10·8 g.), m. p. 130—131°, needles from ethanol–ether (Found: C, 52·3; H, 6·6; N, 5·2. $C_{12}H_{18}O_3NSCl$ requires C, 52·3; H, 6·6; N, 5·1%). *S-Benzylthiothreonine methyl ester hydrochloride B* was similarly prepared as needles, m. p. 171° (Found: C, 52·6; H, 6·8; N, 5·4%).

*N-Thiobenzoyl-*DL*-allothreonine and its Methyl Ester.*—DL-*allo*Threonine methyl ester hydrochloride (4·05 g.) in pyridine (25 ml.) was treated with triethylamine (13·7 ml.), followed by thiobenzoylthioacetic acid (6·7 g.) in pyridine (30·5 ml.). After 24 hr. the addition of cold dilute sulphuric acid gave an oil which was extracted into ether, washed with aqueous sodium hydrogen carbonate, and dried. Evaporation left an oil which crystallised from ether–light petroleum to give the *N-thiobenzoyl-*DL*-allothreonine methyl ester* as pale yellow prisms (3·7 g. 48%), m. p. 66—67° (Found: C, 56·6; H, 6·4; N, 5·7. $C_{12}H_{15}O_3NS$ requires C, 57·0; H, 6·0; N, 5·5%).

The ester (0·5 g.) was dissolved in methyl alcohol (5·0 ml.), and N-sodium hydroxide (2·5 ml.) added. After 24 hr. N-hydrochloric acid (2·5 ml.) was added and the product extracted into ethyl acetate. Concentration and addition of light petroleum (b. p. 60—80°) gave cream-coloured prisms, m. p. 137—138° (decomp.), of *N-thiobenzoyl-*DL*-allothreonine* (Found: C, 55·7; H, 6·0; N, 6·0. $C_{11}H_{13}O_3NS$ requires C, 55·3; H, 5·5; N, 5·9%).

Methyl trans*-5-Methyl-2-phenylthiazoline-4-carboxylate Hydrochloride.*—*N*-Thiobenzoyl-DL-*allo*threonine methyl ester (4·2 g.) was added in portions with shaking to thionyl chloride (10 ml.)

at 0°. After 30 min. the excess of thionyl chloride was removed under reduced pressure and the residue re-evaporated with dry chloroform. The buff solid obtained crystallised from chloroform–light petroleum (b. p. 60—80°), to give the *thiazoline ester hydrochloride* as needles (2·4 g., 53%), m. p. 165—167° softening at 160° (Found: C, 53·0; H, 5·1; N, 5·6. $C_{12}H_{14}O_2NSCl$ requires C, 52·9; H, 5·2; N, 5·2%). The *picrate* separated from water containing a little alcohol as yellow prisms, m. p. 183—184° (decomp.) (Found: C, 46·5; H, 3·7; N, 12·5. $C_{18}H_{16}O_9N_4S$ requires C, 46·6; H, 3·5; N, 12·1%).

trans-N-*Benzoyl*-S-*benzylthiothreonine and its Identity with the A-Series.*—Methyl *trans*-5-methyl-2-phenylthiazoline-4-carboxylate hydrochloride (4·2 g.) and 3N-hydrochloric acid (100 ml.) were refluxed for 4 hr. under nitrogen, the benzoic acid which crystallised on cooling was extracted into ether, and the aqueous layer evaporated to a gum which was repeatedly evaporated with dry benzene under nitrogen. The gum, suspended in chloroform (30 ml.), was treated with triethylamine (2·0 ml.), giving crude thiothreonine (1·35 g. 63%), m. p. 184—186° (decomp.), which gave a strong violet colour with sodium nitroprusside reagent.

The crude thiothreonine (0·95 g.) in liquid ammonia (50 ml.) was treated with sodium until a permanent deep blue colour was obtained which was then removed with a trace of solid ammonium chloride. Benzyl chloride (0·85 ml.) was added and the ammonia allowed to evaporate overnight, to give a solid which was suspended in hot water (10 ml.) and brought to pH 6 with 3N-hydrochloric acid. The *S*-benzylthiothreonine (1·25 g. 80%), m. p. 171—173°, was collected and washed with water. It gave no reaction for a free thiol group.

The foregoing product (1·2 g.), dissolved in N-sodium hydroxide (12·0 ml.), was shaken with benzoyl chloride (0·7 ml.) for 15 min. Acidification gave a cream-coloured solid (1·6 g., 91%) which was extracted with light petroleum (2 × 10 ml.). The residue crystallised from aqueous methyl alcohol to give needles of the A-series product, m. p. 140—142°, not depressed on admixture with the product described by Carter *et al.*[2] (see above.).

β-iso*Propylcysteine Methyl Ester Hydrochloride.*—Methyl 5-*iso*propylthiazolidine-4-carboxylate (10·5 g.) and mercuric chloride (35 g.) reacted in methanol (120 ml.) as described above for the 5-methyl analogue, to give β-iso*propylcysteine methyl ester hydrochloride* (10·1 g.) as needles, m. p. 169—170° (decomp.) (from methanol–ether) (Found: C, 39·3; H, 7·4; N, 6·8; S, 15·0. $C_{17}H_{16}O_2NSCl$ requires C, 39·3; H, 7·6; N, 6·6; S, 15·0%).

NS-*Dibenzoyl*-β-iso*propylcysteine Methyl Ester.*—The above ester hydrochloride (2·1 g.) was shaken with N-sodium hydroxide (32 ml.) and benzoyl chloride (2 ml.), the gum which separated was extracted with chloroform, and the extracts were washed with water and dried. Evaporation of the chloroform gave an oil which crystallised under light petroleum. Recrystallisation from ethanol–light petroleum gave the NS-*dibenzoyl derivative* (1·0 g.) as needles, m. p. 96—97° (Found: C, 65·2; H, 6·4; N, 3·6; S, 8·3. $C_{21}H_{23}O_4NS$ requires C, 65·5; H, 6·0; N, 3·6; S, 8·4%). The same product was formed even if only half the quantity of benzoyl chloride was used.

β-iso*Propylcysteine Amide Hydrochloride.*—5-*iso*Propylthiazolidine-4-carboxyamide (5 g.), mercuric chloride (25 g.), and methanol (300 ml.) were treated as described above for the analogous acid, to give β-iso*propylcysteine amide hydrochloride* (1·5 g.), m. p. 179—181° (decomp.) (Found: C, 36·5; H, 7·4; N, 14·1. $C_6H_{13}ON_2SCl$ requires C, 36·2; H, 7·6; N, 14·0%).

2 : 2-*Dimethyl*-5-iso*propylthiazolidine*-4-*carboxyamide Hydrochloride.*—β-*iso*Propylcysteine amide hydrochloride (1·0 g.), methanol (10 ml.) and acetone (10 ml.) were heated at 100° for 10 min. Concentration and addition of acetone gave the *thiazolidine hydrochloride* (0·8 g.), needles, m. p. 199—200° (decomp.) (from methanol–acetone) (Found: C, 45·5; H, 7·8; N, 11·9. $C_9H_{19}ON_2SCl$ requires C, 45·2; H, 8·0; N, 11·7%).

β-iso*Propylcysteine Hydrochloride.*—β-*iso*Propylcysteine methyl ester hydrochloride (1·5 g.), concentrated hydrochloric acid (7 ml.), and water (20 ml.) were refluxed for 3 hr. under carbon dioxide. Evaporation under reduced pressure gave an oil which was evaporated twice with alcohol and dry benzene; it then crystallised. Recrystallisation from dry alcohol–chloroform–light petroleum gave β-iso*propylcysteine hydrochloride hydrate* as needles, m. p. 142—144° (softening at *ca.* 90°) (Found: C, 33·7; H, 7·7; S, 14·9. $C_6H_{14}O_2NSCl,H_2O$ requires C, 33·0; H, 7·4; S, 14·7%). Drying for 14 hr. at 78°/15 mm. gave the anhydrous form, m. p. 180—182° (lit.,[3] m. p. 197—199°) (Found: C, 35·4; H, 7·4; N, 6·7. Calc. for $C_6H_{14}O_2NSCl$: C, 36·0; H, 7·1; N, 7·0%).

2 : 2-*Dimethyl*-5-iso*propylthiazolidine*-4-*carboxylic Acid Hydrochloride.*—β-*iso*Propylcysteine hydrochloride (0·45 g.) was refluxed in acetone (20 ml.) until dissolved, and the solution cooled,

XUM

the product then separating (0·4 g.). Filtration followed by crystallisation from acetone–alcohol gave the *thiazolidine* as needles, m. p. 202—204° (decomp.) (Found: C, 45·3; H, 7·6; S, 13·5. $C_9H_{18}O_2NSCl$ requires C, 45·0; H, 7·6; S, 13·3%).

ββ-*Dimethylcysteine Methyl Ester Hydrochloride.*—Methyl 5 : 5-dimethylthiazolidine-4-carboxylate (15 g.) and mercuric chloride (15 g.) were allowed to react in methanol (150 ml.) as described above for the 5-methyl analogue, to give ββ-dimethylcysteine methyl ester hydrochloride as needles (8·0 g), m. p. 169—171° (lit., m. p. 173—175°) (from methanol–ether) (Found: C, 36·6; H, 7·2; N, 7·4. Calc. for $C_6H_{14}O_2NSCl$: C, 36·1; H, 7·1; N, 7·0%).

2 : 2 : 5 : 5-*Tetramethylthiazolidine-4-carboxylic Acid.*—ββ-Dimethylcysteine methyl ester hydrochloride (4·3 g.) was refluxed with 5N-hydrochloric acid (60 ml.) under nitrogen for 3 hr. and the solution evaporated to a colourless gum. After re-evaporation twice with dry benzene the crude ββ-dimethylcysteine hydrochloride (4·5 g.) was refluxed in acetone (100 ml.) for 0·5 hr. and cooled, to give the thiazolidine hydrochloride (3 g.), m. p. 208—209° (decomp.) (lit., m. p. 191—194°), needles (from acetone–alcohol) (Found: C, 42·2; H, 7·3; N, 6·2; Cl, 15·7. Calc. for $C_8H_{16}O_2NSCl$: C, 42·6; H, 7·2; N, 6·2; Cl, 15·7%).

S-*Methylthiocarbonylpenicillamine Hydrochloride.*—5 : 5-Dimethyl-2-methylthiothiazoline-4-carboxylic acid (3 g.), concentrated hydrochloric acid (10 ml.), and water (10 ml.) were refluxed for 3 hr. under carbon dioxide. Evaporation gave a syrup which solidified under ethanol, was filtered off, and crystallised from ethanol to give S-*methylthiocarbonylpenicillamine hydrochloride* (2·0 g.), m. p. 186—187° (decomp.) (Found: C, 32·9; H, 5·3; N, 5·8; Cl, 13·8. $C_7H_{14}O_3NS_2Cl$ requires C, 32·3; H, 5·4; N, 5·4; Cl, 13·7%).

5 : 5-*Dimethyl-2-oxothiazolidine-4-carboxylic Acid.*—(1) *S*-Methylthiocarbonylpenicillamine hydrochloride (0·26 g.) in aqueous N-sodium hydroxide (3 ml.) was left at room temperature for 3 hr., then neutralised with N-hydrochloric acid (3 ml.). After concentration the colourless precipitate was separated and crystallised from water to give the thiazolidone as needles, m. p. 180—181°, identical (mixed m. p.) with that prepared by Cook, Elvidge, and Shaw's method [18] (Found: C, 40·9; H, 5·2; N, 8·1. Calc. for $C_6H_9O_3NS$: C, 41·1; H, 5·2; N, 8·0%)

(2) 5 : 5-Dimethyl-2-thiothiazolidine-4-carboxylic acid (2 g.) and chloroacetic acid (4 g.) in water (20 ml.) were refluxed for 4 hr. After 24 hr. at room temperature the solution was concentrated *in vacuo* and the precipitate separated. Crystallisation from water gave the thiazolidone as needles, m. p. and mixed m. p. 182—183°.

The authors of this and the preceding four papers thank Sir Ian Heilbron and Dr. A. H. Cook for their interest, Dr. L. J. Edwards for the ultraviolet spectra, and Mrs. J. Mamalis and staff for the microanalyses.

Beecham Research Laboratories, Limited,
Brockham Park, Betchworth, Surrey.

[*Received, July 7th,* 1958.]

---

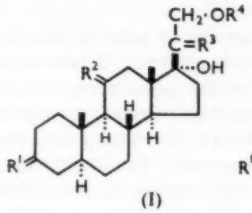
930. *Use of* 20-*Oximes and* 20-*Semicarbazones in making Cortisol and* 4 : 5α-*Dihydrocortisol.*

By S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and L. J. Wyman.

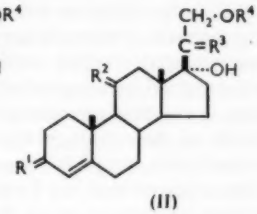
Experiments leading to satisfactory conversion of cortisone and its 21-acetate into cortisol, and of 4 : 5α-dihydrocortisone acetate into 4 : 5α-dihydrocortisol, have confirmed the utility of the 3 : 20-dioximes and 3 : 20-disemicarbazones as intermediates; in particular, the newly discovered reactivity of the 21-acetoxy-17α-hydroxy-20-ketones has been exploited. Treatment of the 20-hydroxyimino-steroids with nitrous acid yields nitrimino-compounds, which are probably mesoionic.

In continuing work on the synthesis of cortical hormones from 5α-steroids we have sought means of making cortisol and related 9α-halogeno-derivatives. Of various approaches open, the most attractive uses 4 : 5α-dihydrocortisone acetate (I; $R^1 = R^2 = R^3 = O$, $R^4 = Ac$) and its reduction product 4 : 5α-dihydrocortisol (I; $R^1 = R^3 = O$, $R^2 = H$, β-OH,

R^4 = H). A method for making the latter compound has already been described;[1] we discuss in this paper improved methods for this and related purposes.



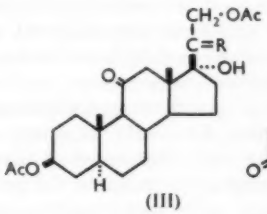
(I)



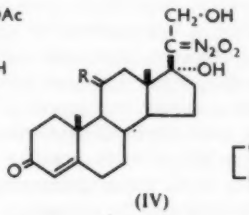
(II)

4:5α-Dihydrocortisone: $R^1 = R^2 = R^3 = O$, $R^4 = H$
4:5α-Dihydrocortisol: $R^1 = R^3 = O$, $R^2 = H$, β-OH, R = H
Substance D: $R^1 = H$, β-OH, $R^2 = R^3 = O$, $R^4 = H$; cf. (III)

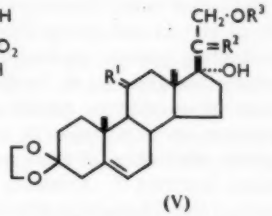
Cortisone: $R^1 = R^2 = R^3 = O$, $R^4 = H$
Cortisol: $R^1 = R^3 = O$, $R^2 = H$, β-OH, $R^4 = H$
Substance S: $R^1 = R^2 = O$, $R^3 = H_2$, $R^4 = H$



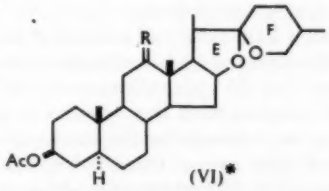
(III)



(IV)



(V)



(VI)*

* Compounds with the same configuration in rings E and F as in tigogenin.
When R in (IV), and R^1 in (V) are H, OH, the 11β-hydroxy-group is implied.

Reduction of 3 : 11 : 20-trioxo-steroids to 11β-hydroxy-3 : 20-diones calls for selective protection at the 3- and the 20-position. Our experience confirms the difficulties in the acid-catalysed formation of ketals[1] and semicarbazones[2] of the 21-hydroxy-ketones, and earlier work proved the lack of reactivity of the 21-acetoxy-ketones.[3] However, one exception is noteworthy, for Reichstein's substance D 3 : 21-diacetate with semicarbazide base in hot acetic acid gave the derivative (III; R = N·NH·CO·NH_2), whereas pure 20-semicarbazones were not obtainable by this method from other 21-acetoxy-17α-hydroxy-20-ketones. We had recourse therefore to base-catalysed condensations with semicarbazide and hydroxylamine solutions,[4] utilising a tertiary base, preferably pyridine, as

[1] Evans, Green, Hunt, Long, Mooney, and Phillipps, *J.*, 1958, 1529.
[2] Wendler, Huang-Minlon, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 3818; cf. Wintersteiner and Pfiffner, *J. Biol. Chem.*, 1936, **116**, 291.
[3] Mancera, *J. Amer. Chem. Soc.*, 1950, **72**, 5752; Bernstein, Antonucci *et al.*, *J. Org. Chem.*, 1952, **17**, 1369; 1953, **18**, 70; Constantin, Haven, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 1716; Ralls and Riegel, *ibid.*, 1954, **76**, 4479; Sondheimer, Mancera, and Rosenkranz, *ibid.*, p. 5020; cf. Fleisher and Kendall, *J. Org. Chem.*, 1951, **16**, 556; von Euw, Neher, and Reichstein, *Helv. Chim. Acta*, 1955, **38**, 1423; ref. 2.
[4] Jones and Robinson, *J. Org. Chem.*, 1956, **21**, 586; Oliveto, Rausser, Weber, Shapiro, Gould, and Hershberg, *J. Amer. Chem. Soc.*, 1956, **78**, 1736; Joly, Nominé *et al.*, *Bull. Soc. chim. France*, 1956, 837, 1459.

XUM

solvent and catalyst.[5] Such conditions promote efficient condensations, even with the 21-acetoxy-ketones, and the semicarbazones so produced can be efficiently hydrolysed with solutions containing pyruvic acid [6] or, better, with mixtures of aqueous mineral acid and a solvent only slightly soluble in water.[7]

Comparison of the properties of the semicarbazones is made difficult by their insolubility and tendency to become solvated; further, attempted acetylation of the 20-semicarbazono-21-alcohols may be accompanied by removal of the basic group.[8] The infrared absorption due to the acetate group in the 21-acetoxy-semicarbazones is poorly resolved, but analyses and controlled hydrolysis of these compounds to 21-acetoxy-20-ketones prove that they are formed and hydrolysed with complete retention of the 21-acetate group. Present and already published evidence shows that the 11-keto-group does not form a semicarbazone,[9] and attempts at making a derivative of 3β-acetoxyergost-22-en-11-one failed. The 20-semicarbazones have $\lambda_{max.}$ 240 mμ, which coincides with the band due to a saturated 3-semicarbazone or may appear only as a shoulder in the absorption curve due to a Δ^4-3 : 20-disemicarbazone.

This method of using basic media to form the 3 : 20-disemicarbazones, with subsequent reduction of the 11-oxo-group with a borohydride [2,4] and final acid-catalysed removal of the protecting groups, yielded efficient conversions of 4 : 5α-dihydrocortisone acetate and cortisone acetate into 4 : 5α-dihydrocortisol and cortisol respectively.

Tertiary bases such as pyridine might be expected to affect condensations with hydroxylamine, semicarbazide, or *O*-methylhydroxylamine differently, inasmuch as they would favour production of the ion $NH_2 \cdot O^-$; in practice such differences, if they exist, are of small account.[10] Evidence from paper chromatography indicates the possibility of oximating the 21-acetoxy-17α-hydroxy-20-oxo-system with acetic acid as catalyst, but only in conditions giving by-products.

Blatt [11] has shown that base-catalysed oximation favours the most strongly hydrogen-bonded forms of the derivatives of *o*-hydroxy-ketones in the aromatic series, and Schmidt-Thomé [12] has suggested that 20-hydroxyimino-steroids assume a configuration allowing the strongest hydrogen bonding with the substituent at the 21-position. In accordance with these observations our evidence for the existence of *syn*- and *anti*-forms comes only from the behaviour of the oxime *O*-methyl ethers and *O*-acetates (see Table 2), and the infrared spectra of the 20-hydroxyimino-21-acetates reveal marked intramolecular hydrogen bonding. We have not detected geometrical isomerism among the 3-oximes.[13] Analysis of the properties of the semicarbazones and oximes discloses inconsistent increments in molecular rotation, but good agreement in the ΔR_M values [14] for the oxime groups, except among the derivatives of cortisone. One of the last-named compounds, the dioxime (II; $R^1 = R^3 = N \cdot OH$, $R^2 = O$, $R^4 = H$), is also exceptional in the ease with which its 11-keto-group is reduced (see below). In view of the marked influence [3] of the 21-acetate group on reactions involving the 20-ketones and on the stability of the 20-nitrimines (see below), its minor or erratic effect on the physical properties of the 20-oximes and 20-semicarbazones is surprising.

[5] Hopper, *J. Roy. Tech. Coll. Glasgow*, 1929, **2** (i), 52; Haller and La Forge, *J. Org. Chem.*, 1936, **1**, 38; Gulati and Ray, *Current Sci.*, 1936, **5**, 75; Jacquemain and Galliot, *Ann. Chim.*, 1946, **1**, 262; Greer and Pearson, *J. Amer. Chem. Soc.*, 1955, **77**, 6649; Campbell, McCallum, and Mackenzie, *J.*, 1957, 1922; cf. Cook, Hewett, and Lawrence, *J.*, 1936, 71.

[6] McGuckin and Kendall, *J. Amer. Chem. Soc.*, 1952, **74**, 5811.

[7] Kapp and Griffith, U.S.P. 2,530,334; Day, U.S.P. 2,781,367.

[8] Wolfrom, Georges, and Soltzberg, *J. Amer. Chem. Soc.*, 1934, **56**, 1794; Turner, *ibid.*, 1947, **69**, 875; Oliveto, Herzog, Weber, Tully, and Hershberg, *J. Org. Chem.*, 1956, **21**, 795.

[9] Cf. Elks and Phillipps, *J.*, 1956, 4326.

[10] Cf. Ingold, "Structure and Mechanism in Organic Chemistry," Bell and Sons Ltd., London, 1953, p. 688.

[11] Blatt, *J. Org. Chem.*, 1955, **20**, 591 and earlier papers.

[12] Schmidt-Thomé, *Chem. Ber.*, 1955, **88**, 895.

[13] Cf. Ralls, *J. Amer. Chem. Soc.*, 1938, **60**, 1744; 1940, **62**, 2459.

[14] Brooks, Hunt, Long, and Mooney, *J.*, 1957, 1175.

Reduction of cortisone dioxime (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = O$, $R^4 = H$) with a borohydride is claimed in a patent [15] to give the dioxime of cortisol. However, the properties cited for the latter compound did not agree with those of the dioxime we made from cortisol, and we therefore studied the reduction of cortisone 3 : 20-dioxime and its 21-acetate. Paper chromatography of the products from the reduction of the 21-acetate with sodium borohydride showed that the ester was hydrolysed almost immediately and the ketone reduced with unexpected rapidity; generation of cortisol dioxime was accompanied by other reactions producing at least two contaminants, and indeed the yield of the required compound from such reductions was poor. Use of lithium borohydride in non-aqueous solvents gave from the dioxime of cortisone, or its 21-acetate, " infusible " material (m. p. >300°) with properties like those attributed in the patent to cortisol 3 : 20-dioxime. We found that this substance contained boron, which could be removed when it was heated in refluxing methanol,[16] with the production of the 3 : 20-dioxime also generated directly from cortisol.

The nature of such boron-containing substances, which have also been noticed in the reduction of 3 : 20-dioximes methyl ethers, is not clear, and we have not studied them further. Nevertheless, knowledge gained in the foregoing experiments made possible an efficient conversion of cortisone into cortisol, the oxime groups being removed from the reduction product either by persulphuric acid or by nitrous acid with subsequent hydrolysis of the 20-nitrimine (IV; R = H, β-OH) (see below). Cortisone 3 : 20-dioxime dimethyl ether (II; $R^1 = R^3 = N{\cdot}OMe$, $R^2 = O$, $R^4 = H$) could also be reduced; the product, the cortisol derivative (II; $R^1 = R^3 = N{\cdot}OMe$, $R^2 = H$, β-OH, $R^4 = H$), slowly yielded cortisol on acid-catalysed hydrolysis.

Further adaptation of the properties of the new 20-oximes exploited the ease of hydrolysing them and the 3 : 3-ethylenedioxy-group [1] in dilute acid. The ketals of cortisone and its 21-acetate (V; $R^1 = R^2 = O$, $R^3 = H$ and Ac) gave 20-oximes, convertible into cortisol by borohydride reduction and subsequent acid-catalysed hydrolysis of both protecting groups.

Attempts at regenerating cortisone acetate and similar 3 : 11 : 20-triones from their 3 : 20-dioximes showed that the action of aqueous mineral acid is generally limited to hydrolysis of the 20-hydroxyimino-group;[17] however, the 3- and the 20-oximes can be hydrolysed by aqueous persulphuric acid with simultaneous extraction of the ketones into methylene chloride. Persulphuric acid assists the hydrolysis by oxidising the liberated hydroxylamine;[18] in similar conditions or with dilute hydrochloric acid the hydrolysis of the 3 : 20-dioxime dimethyl ethers was completed very slowly. Aldehydes or ketones [6,17] failed to facilitate the hydrolysis in acid solution or in pyridine; sulphurous acid slowly but inefficiently removed the hydroxyimino-groups,[19] and bromine in polar solvents was unsatisfactory.[20] Nitrous acid regenerated the 3-oxo-group,[21] but converted the 20-hydroxyimino-groups into nitrimino-groups, recognisable in particular by their intense absorption at 1305—1330 and 1560—1580 cm.$^{-1}$. We have made pure specimens of the derivatives (IV; R = H, β-OH; and R = H_2) of cortisol and Reichstein's substance S and the nitrimine (V; $R^1 = O$, $R^2 = N_2O_2$, $R^3 = H$), but could not obtain their 21-acetates pure, because hydrolysis to the 20-ketone was unavoidable. Prolonged heating

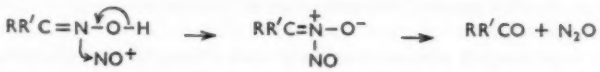
[15] Graber and Wendler, U.S.P. 2,628,966.
[16] Cf. Chaikin and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 122; Abdel-Akker, Hamilton, and Smith, *ibid.*, 1951, **73**, 4691; Reid and Siegel, *J.*, 1954, 520.
[17] Cf. Hershberg, *J. Org. Chem.*, 1948, **13**, 542.
[18] Cf. Partington, " Textbook of Inorganic Chemistry," Macmillan & Co. Ltd., London, 1944, p. 556.
[19] von Pechmann, *Ber.*, 1887, **20**, 2904; Claisen and Manasse, *Ber.*, 1889, **22**, 530; Gluud, *Ber.*, 1915, **48**, 420.
[20] Piloty, *Ber.*, 1897, **30**, 3161; cf. Iffland and Yen, *J. Amer. Chem. Soc.*, 1954, **76**, 4083; Emmons and Pagano, *ibid.*, 1955, **77**, 4557.
[21] Cf. Goldschmidt and Veer, *Rec. Trav. chim.*, 1946, **65**, 796; 1947, **66**, 238; Hey and Morris, *J.*, 1948, 2319; Herzog, Payne, Jevnik, Gould, Shapiro, Oliveto, and Hershberg, *J. Amer. Chem. Soc.*, 1955, **77**, 4781.

XUM

in polar solvents containing water converted the 20-nitrimino-17α : 21-dialcohols into 17α : 21-dihydroxy-20-ketones. Unless the nitrimine crystals were solvated with water, they showed no undue instability at raised temperatures. Attempts at facilitating hydrolysis of the 20-nitrimino-17α : 21-dialcohols by prior acetylation miscarried and caused blackening. Comparison of 3- and 20-monoximes has confirmed that only the latter yield isolable nitrimines, nitrous acid converting the former into ketones with a display of transient colours. Oxime methyl ethers did not give such products.

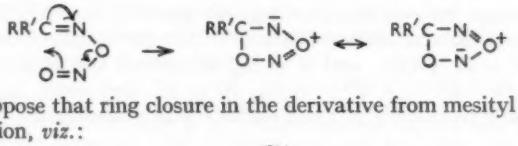
The action of nitrous acid on ketoximes does not generally yield nitrimines: they are generated (or, at least, isolable) only when the carbon atom on one side of the >C=N·OH group lacks hydrogen atoms. The terpenes provide a dozen or so examples and the steroids about half-a-dozen, the latter all 12-nitrimines.[22] In this connexion full substitution on the adjacent carbon atom, hitherto exemplified only with alkyl substituents in saturated and αβ-unsaturated oximes, does not imply a restriction on prototropy, since the terpenoid ketones and 12-oxo-steroids giving nitrimines can be brominated on the carbon atom not fully substituted.[23]

On the basis of differences between the derivatives of saturated and αβ-unsaturated oximes, Scholl [24] and Italian workers [25] have tried to classify the compounds and attribute structures to them. We can now extend the classification, since the nitrimines derived from camphor, hecogenin acetate, and the 20-oxo-steroids, which are hydrolysed to the parent ketones, display a pattern in their infrared absorption not obvious in the spectrum of the derivative of mesityl oxide, which is hydrolysed to the oxime or to other nitrogen-containing products. An attempted proof [26] of the structure >C=N·NO_2 for the camphor-derivative and its congeners being in our opinion inconclusive, we are tempted to speculate on the manner in which the ion NO^+ attacks the oximes. We assume that its usual action (for example, on 3-hydroxyimino-steroids) can be represented as an attack on the nitrogen atom:

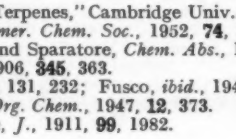


In heavily substituted oximes approach to the nitrogen atom may be hindered, so that attack at the oxygen atom predominates:

Subsequent cyclisation may then generate a mesoionic system, which offers a modern form of an expression first proposed by Foster, Trotter, and Weintroube [27] for the nitrimines:



We would then suppose that ring closure in the derivative from mesityl oxide is balked by the electron-accession, *viz.*:



[22] *E.g.*, Schenck and Reschke, *Ber.*, 1940, **73**, 200; Schenck, *Ber.*, 1942, **75**, 198; 1943, **76**, 874; 1944, **77**, 29, 501.
[23] *E.g.*, Simonsen and Owen, "The Terpenes," Cambridge Univ. Press, 1949, Vol. II, pp. 395 *et seq.*; Hershberg, Gerold, and Oliveto, *J. Amer. Chem. Soc.*, 1952, **74**, 3849; Elks, Phillipps, Walker, and Wyman, *J.*, 1956, 4330; cf. Gandini and Sparatore, *Chem. Abs.*, 1956, **50**, 7748.
[24] Scholl, *Annalen*, 1905, **338**, 1; 1906, **345**, 363.
[25] *E.g.*, Gandini, *Gazzetta*, 1942, **72**, 131, 232; Fusco, *ibid.*, 1943, **73**, 36.
[26] Suggitt, Myers, and Wright, *J. Org. Chem.*, 1947, **12**, 373.
[27] Foster, Trotter, and Weintroube, *J.*, 1911, **99**, 1982.

the powerfully hyperconjugative methyl groups in the nitrimine derived from pinacolone, which behaves like the unsaturated compound, probably stabilise the ester form similarly. The derivative of santonin has also been regarded as an oxime ester.[28]

A cyclic structure for nitrimines derived from ketones such as camphor satisfactorily accommodates their lack of colour, their hydrolysis to ketones, and the reduction of camphor nitrimine to bornylamine and *iso*bornylamine.[29] For the time being we are keeping the name nitrimine although, like the prefix pernitroso-, it no longer retains its precise meaning when applied to the compounds discussed herein.

Experimental

For general procedures see earlier papers.[1,14] In this paper the following conditions were observed, unless others are mentioned: m. p.s for samples on a Kofler block; optical rotations for semicarbazones in pyridine, for oximes and nitrimines in dioxan, and for other compounds in chloroform, all solutions being about 1% and at 20° ± 3°; infrared and ultraviolet absorption spectra for specimens in Nujol mulls and ethanolic solution respectively. The m. p.s of the semicarbazones vary according to the conditions and occur with darkening and decomposition at >200°; solid compounds whose m. p.s are not given melt at >300°. The m. p.s of the 20-oxo-17 : 21-dialcohols depend greatly on the size of the particles.[30] In the infrared spectra the semicarbazones showed peaks at 1680 and 1570, the oximes at 1645—1625, and the nitrimines at 1560—1580 and 1305—1330 cm.$^{-1}$. (See also the description below of the derivatives of mesityl oxide.)

The oximes and semicarbazones were prone to solvation, which was very difficult to reverse. Difficulties in combustion also made their analysis troublesome.[31]

The 20-oximes and 20-semicarbazones gave no colour with the TSTZ reagent (see below) and the rate of their formation could be confirmed by this test and polarimetry. Due allowance must be made for the colour given by hydroxylamine and semicarbazide with the TSTZ reagent;[32] *O*-methylhydroxylamine gave no colour. The identities of reaction products were confirmed by spectroscopy and paper chromatography.

Paper Chromatography.—The parent compounds and the oximes were run at 30° on Whatman No. 2 papers, with the following solvents (unless a system is mentioned, solvent L was used):

Solvent system	Light petroleum, b. p. 60—80°	Methanol	Toluene	Water	Dioxan	Benzene
L	75	200	325	75	—	—
M	—	200	200	100	25	—
N	—	55	—	45	—	100

The fractions were located with a spray consisting of a 1% solution of 2 : 5-diphenyl-3-*p*-styrylphenyltetrazolium chloride (M and B 1767, May and Baker Ltd., Dagenham) in ethanol diluted with water (4 parts); just before use this solution was mixed with half its volume of aqueous 10% sodium hydroxide. The spots reached their maximum intensity after about 10 min. at room temperature; the papers were best kept in the dark. The foregoing is referred to in this paper as the TSTZ reagent.

Compounds not giving colours with this reagent were detected by examination in ultraviolet light[33] or by the Komarowsky reagent[34] or with vanillin and perchloric acid.[35]

In the following list the R_M values (°)[14] for each 21-alcohol and its 21-acetate and the ΔR_M value for the esterification are given in that order: substance S, −0·04, −0·87, −0·83; cortisone 0·63, −0·37, −1·00; cortisol, 0·91, −0·05, −0·96; 4 : 5α-dihydrocortisone, 0·31, −0·50, −0·81; 4 : 5α-dihydrocortisol, 0·58, −0·37, −0·95. The average ΔR_M for 21-acetylation is therefore −0·91 ±0·10. Values of ΔR_M for several other conversions are as follows: formation

[28] Simonsen and Barton, "The Terpenes," Cambridge Univ. Press, 1952, Vol. III, p. 270.
[29] Simonsen and Owen, ref. 23, p. 441.
[30] Reichstein and Shoppee, *Vitamins and Hormones*, 1943, **1**, 345.
[31] Cf. Ramirez and Stafiej, *J. Amer. Chem. Soc.*, 1955, **77**, 134; Davison and Christie, *J.*, 1955, 3389; Fabian, Legrand, and Poirier, *Bull. Soc. chim. France*, 1956, 1499.
[32] Snow, *J.*, 1954, 2588; Rogers, *J.*, 1955, 769.
[33] Bush, *Biochem. J.*, 1952, **50**, 370.
[34] Callow, Dickson, Elks, Evans, James, Long, Oughton, and Page, *J.*, 1955, 1966.
[35] Godin, *Nature*, 1954, **174**, 134.

XUM

of 3 : 20-dioxime dimethyl ethers (in Δ^4-steroids), −1·37 (±0·10); 20-nitrimine formation, 0·25 (±0·04); 3-oximation in Δ^4-steroids, 0·50 (±0·07), and in 5α-steroids (indirect calculation), 0·5—0·6; 20-oximation, 0·63 (±0·02); 3 : 20-dioximation (in Δ^4-steroids), 1·12 (±0·04). Except for the oximation of cortisone these reactions gave consistent increments.

The following R_F values were obtained with system L (the compound marked * being an otherwise unidentified component of mixtures). (*a*) Substance S, 0·52; 3-oxime, 0·28; 3 : 20-dioxime, 0·08; 3 : 20-dioxime dimethyl ether, 0·97; 20-nitrimine, 0·40. (*b*) Substance S 21-acetate, 0·88; 3-oxime,* 0·44; 3 : 20-dioxime, 0·34. (*c*) Substance D 3 : 21-diacetate, 0·93; 20-oxime, 0·76. (*d*) 4 : 5α-Dihydrocortisone 21-acetate, 0·76; 3 : 20-dioxime, 0·09. (*e*) Cortisone, 0·19; 3-oxime, 0·07; 3 : 20-dioxime, 0·10. (*f*) Cortisone 21-acetate, 0·70; 3-oxime, 0·44; 3 : 20-dioxime, 0·10. (*g*) Cortisol, 0·11; 3-oxime, 0·04; 3 : 20-dioxime, 0·01; 3 : 20-dioxime dimethyl ether, 0·69; 20-nitrimine, 0·06.

Solvents M and N give higher R_F values.

Preparation of Semicarbazones.—The following description is of a typical example. Cortisone acetate (1 g.), dissolved in pyridine (25 ml.), was mixed with a solution of semicarbazide hydrochloride (5·4 g.) in water (6 ml.) to which a cool mixture of pyridine (25 ml.) and concentrated hydrochloric acid (6·2 ml.) had been added. The α decreased from +5·60° (after 1·75 min.) to +5·12° (64 hr.) (1 dm. tube), and then stayed constant. Aqueous sodium acetate was then added to neutralise the hydrochloric acid, and most of the solvents were evaporated off. Dilution with water then precipitated the disemicarbazone (1·23 g., 93%) (see Table 1). β-Picoline or *NN*-dimethylaniline could be used instead of pyridine.

Formation of the 20-semicarbazones of 17α : 21-dihydroxy-20-ketones was complete in <48 hr. Such products were purer than those made with acid catalysis.[2] 3β-Acetoxyergost-22-en-11-one was not converted into a semicarbazone, even after prolonged treatment in these conditions.

The 3-monosemicarbazones were obtained by terminating the condensation when the rotation reached its maximum (generally <5 min.). They were also made satisfactorily with the base hydrochloride and sodium acetate[36] or by the procedure typified in the following example. Semicarbazide hydrochloride (1 g.; finely ground) in *NN*-dimethylformamide (10 ml.) and pyridine (5 ml.) was added to cortisone acetate (0·5 g.) in pyridine (11 ml.). The

TABLE 1. *Properties of semicarbazones.*

(a) 3 : 20 - *Disemicarbazones* ($R^1 = R^3 = N{\cdot}NH{\cdot}CO{\cdot}NH_2$) of:

4 : 5α-*Dihydrocortisone* (I; $R^3 = O$, $R^4 = H$), $[\alpha]_D$ +17°, $\lambda_{max.}$ 229 mμ (ε 22,860) (Found: N, 16·7. $C_{23}H_{36}O_5N_6$,1·5H_2O requires N, 16·7%); 21-*acetate* (I; $R^3 = O$, $R^4 = Ac$), $[\alpha]_D$ +21°, $\lambda_{max.}$ 231 mμ (ε 24,250) (Found: C, 54·5; H, 7·75; N, 15·5; OAc, 8·1. $C_{25}H_{38}O_6N_6$,1·5H_2O requires C, 55·0; H, 7·6; N, 15·4; OAc, 7·9%).

17α : 21-*Dihydroxypregn*-4-*ene*-3 : 20-*dione* (substance S, II; $R^3 = H_2$, $R^4 = H$), $[\alpha]_D$ +113°, $\lambda_{max.}$ 269 mμ (ε 34,100) (Found: C, 59·4; H, 8·1; N, 18·2. $C_{23}H_{36}O_4N_6$ requires C, 60·0; H, 7·9; N, 18·25%); 21-*acetate* (II; $R^3 = H_2$, $R^4 = Ac$), $[\alpha]_D$ +108°, $\lambda_{max.}$ 269 mμ (ε 34,100) (Found: C, 58·2; H, 7·7; N, 16·35; OAc, 8·1. $C_{25}H_{38}O_5N_6$,0·5H_2O requires C, 58·75; H, 7·7; N, 16·4; OAc, 8·4%).

Cortisone (II; $R^3 = O$, $R^4 = H$), $[\alpha]_D$ +195°, $\lambda_{max.}$ 270 mμ (ε 31,200), shoulder at 240 mμ (ε 19,500) (Found: N, 17·2. Calc. for $C_{23}H_{34}O_5N_6$: N, 17·7%);[2] 21-acetate (II; $R^3 = O$, $R^4 = Ac$), $[\alpha]_D$ +206°, $\lambda_{max.}$ 242·5 (ε 22,400) and 269 mμ (ε 28,950) (Found: C, 56·6; H, 7·3; N, 16·1; OAc, 8·1. Calc. for $C_{25}H_{36}O_6N_6$,0·5H_2O: C, 57·15; H, 7·1; N, 16·0; OAc, 8·3%).[4]

(b) 3-*Monosemicarbazones* ($R^1 = N{\cdot}NH{\cdot}CO{\cdot}NH_2$, $R^3 = O$, $R^4 = Ac$) of:

21-*Acetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione* (II; $R^3 = H_2$), $[\alpha]_D$ +157°, $\lambda_{max.}$ 269 mμ (ε 30,500) (Found: N, 9·2. $C_{24}H_{35}O_5N_3$,0·5H_2O requires N, 9·25%).

Cortisone 21-acetate (II; $R^3 = O$), $[\alpha]_D$ +252° (in dioxan), $\lambda_{max.}$ 270 mμ (ε 30,800) (Found: N, 8·8. Calc. for $C_{24}H_{33}O_6N_3$,0·5H_2O: N, 9·0%) (crystallised from ethanolic methylene dichloride).[6]

α (0·5 dm. tube) +2·66° became 3·00° (constant) in 1 hr. The solution was diluted with water, and the precipitated semicarbazone (II; $R^1 = N{\cdot}NH{\cdot}CO{\cdot}NH_2$, $R^3 = R^3 = O$, $R^4 = Ac$) was collected.

A special procedure for use with substance D diacetate (III; R = O) is described below. We failed to make identifiable derivatives of the 20-ketones with Girard's reagents.[37]

The properties of the semicarbazones made in this work are listed in Table 1. They were

[36] Wild, "Characterisation of Organic Compounds," Cambridge Univ. Press, 1948, p. 121.
[37] Cf. McKinley, *Science*, 1955, **121**, 139.

all made in nearly quantitative yield. The 21-alcohols separated pure from aqueous pyridine; all the 21-acetates separated as needles from methanol.

Hydrolysis (see below) in high yield of representative semicarbazones to the parent ketones confirmed the structures of the derivatives.

3β : 21-*Diacetoxy*-17α-*hydroxy*-20-*semicarbazono*-5α-*pregnan*-11-*one* (III; R = N·NH·CO·NH_2).—(i) The diacetate (III; R = O) (1 g.) and semicarbazide base (1 g.) in glacial acetic acid (10 ml.) were heated on a steam-bath for 15 min. The cooled mixture was poured into water, and the precipitate (1·12 g.), m. p. 244—246°, was collected. Crystallisation from aqueous acetic acid gave the *semicarbazone* (III; R = N·NH·CO·NH_2), m. p. 252°, $[\alpha]_D$ ±0°, $\lambda_{max.}$ 239·5 mμ (ε 9960) (Found: C, 61·45; H, 7·7; N, 8·0. $C_{26}H_{39}O_7N_3$ requires C, 61·75; H, 7·8; N, 8·3%). (ii) (With Dr. J. Oughton and Mr. L. Stephenson.) The diacetate (III; R = O) (0·50 g.) was shaken for 1 week with pyridine (32·5 ml.), concentrated hydrochloric acid (2·25 ml.), water (2·5 ml.), and ethyl acetate (10 ml.), during which time two phases were formed, the lower yellow. Most of the solvent was distilled off, and water added to the residue to precipitate plates of the semicarbazone (0·527 g., 93%), m. p. 244—246°, $[\alpha]_D$ ±0°, $\lambda_{max.}$ 239·5 mμ (ε 9960), identified with the product described in (i) above. Omission of the ethyl acetate led to the generation of an inferior product, presumably owing to hydrolysis of the 3-acetate.

This semicarbazone (0·50 g.) was hydrolysed by suspension in ethyl acetate (100 ml.) to which 2N-hydrochloric acid (50 ml.) was added. The mixture was stirred at room temperature for 5 hr., during which all the solid dissolved. The aqueous layer was twice extracted with ethyl acetate, and the combined ethyl acetate phases were washed several times with 2N-hydrochloric acid, then with sodium hydrogen carbonate and water. Isolation and crystallisation from ethyl acetate gave prisms (0·34 g., 77%) of the pure diketone (III; R = O), m. p. 218—220°, $[\alpha]_D$ +69° {lit.,[30] m. p. 223—224°, $[\alpha]_D^{15}$ +72°}. Use of methylene dichloride instead of ethyl acetate in the hydrolysis led to the formation of intractable emulsions.

Cortisol from the Disemicarbazone of Cortisone.—The semicarbazone (II; R^1 = R^3 = N·NH·CO·NH_2, R^2 = O, R^4 = H) (3·0 g.), dissolved in *NN*-dimethylformamide (19 ml.) and anhydrous tetrahydrofuran (38 ml.), was added dropwise during 30 min. to lithium borohydride (1·9 g.) suspended in anhydrous tetrahydrofuran (94 ml.). The mixture was stirred at room temperature for another 2 hr., neutralised with aqueous acetic acid, evaporated to small bulk, and then diluted with much water. Part (2·0 g.) of the product (2·14 g.), which gave no colour with the TSTZ reagent, was dissolved in acetic acid (44 ml.), " 50—60% " pyruvic acid (British Drug Houses Ltd.) (7·3 ml.) and pyridine sulphate solution (22 ml.; see below) and stored at room temperature for 17 hr. The solution was then poured into much water, and isolation of the steroid with ethyl acetate gave cortisol (0·94 g., 62%), m. p. 207—214°, $[\alpha]_D$ +157° (in MeOH), $\lambda_{max.}$ 242 mμ (ε 15,400). A second crop (0·11 g., 7%) of m. p. 200—201° was also obtained.

4 : 5α-*Dihydrocortisol* 21-*Acetate.*—The disemicarbazone (I; R^1 = R^3 = N·NH·CO·NH_2, R^2 = O, R^4 = Ac) (5 g.), dissolved in ethanol (500 ml.), methylene dichloride (300 ml.), and water (100 ml.), was treated at room temperature with sodium borohydride (2·5 g.) in water (25 ml.). The solution was then refluxed for 2 hr., and cooled, and the excess of borohydride decomposed with aqueous acetic acid. The solvents were distilled off and the residue was acetylated with acetic anhydride (25 ml.) and pyridine (50 ml.). Evaporation of these left a solid, which was ground in a little water and transferred to a separating funnel. A cool solution of concentrated hydrochloric acid (133 ml.) and water (100 ml.) was added. After 1 minute's stirring the suspension cleared and it was then extracted with batches of ethyl acetate and methylene dichloride (1 : 1; 100 ml. each) until the extracts no longer had optical rotatory power and gave very weak colours with the TSTZ reagent. The washed and dried steroid (3·14 g.) from the combined extracts was acetylated with acetic anhydride (12·5 ml.) and pyridine (25 ml.) for 2 hr. at room temperature, giving a product (3·17 g.) that crystallised from ethyl acetate as 4 : 5α-dihydrocortisol acetate [1] (1·88 g., 48%), m. p. 220—222° (capillary), $[\alpha]_D$ +76°, with a second crop (0·81 g., 21%), m. p. 212—217° (capillary), $[\alpha]_D$ +74°.

Removal of the Semicarbazone Groups by Hydrolysis.—(i) The disemicarbazone (II; R^1 = R^3 = N·NH·CO·NH_2, R^2 = O, R^4 = Ac) (1 g.) of cortisone acetate and " 50—60% " pyruvic acid (British Drug Houses Ltd.) (3·7 ml.) was treated with a solution (11 ml.) of pyridine sulphate, made as follows: concentrated sulphuric acid (20 ml.) was poured into water (20 ml.), and the solution cooled and added slowly to pyridine (62 ml.); finally it was made up to 100 ml. with

water. The solution containing the steroid was kept at room temperature for 5 days, the rotation becoming constant. Dilution with water and extraction with ethyl acetate afforded cortisone acetate (0·815 g.), which crystallised from ethyl acetate to give a pure product (0·61 g., 79%), m. p. 241—244° (capillary), $[\alpha]_D$ +219°. The 3 : 20-disemicarbazones of the following were also hydrolysed in this manner (yields in brackets): 4 : 5α-dihydrocortisone (69%) and its 21-acetate (70%); substance S (66%) and its 21-acetate (81%), and 4 : 5α-dihydrocortisol acetate (48%; see above). Paper chromatography showed that in these circumstances the 21-acetates were not hydrolysed and that less polar compounds were not generally formed.[38]

(ii) This method is exemplified in the preparation of 4 : 5α-dihydrocortisol acetate and in the hydrolysis of the 20-semicarbazone of substance D diacetate (see above). The 3 : 20-disemicarbazones of 4 : 5α-dihydrocortisone 21-acetate (85%) and cortisone 21-acetate (62%) were hydrolysed similarly.

(iii) The powdered disemicarbazone (I; $R^1 = R^3 = N{\cdot}NH{\cdot}CO{\cdot}NH_2$, $R^2 = O$, $R^4 = Ac$) (1 g.) was suspended in water and cooled to 0°. Concentrated hydrochloric acid (20 ml.) mixed with water (5 ml.) was slowly run into the stirred suspension, and then a solution (1·1 ml.) made from sodium nitrite (5·45 g.) and water (10 ml.). Gas evolution subsided after 30 min., but the solution still gave a colour with starch–iodide. Urea was added until this test was negative, the solution diluted with water, and the precipitated steroid filtered off, dried, and acetylated with acetic anhydride (5 ml.) and pyridine (10 ml.). Evaporation and crystallisation of the residue from acetone gave 4 : 5α-dihydrocortisone 21-acetate (0·62 g., 80%), m. p. 224—227° (capillary), $[\alpha]_D$ +98°. This method generally gave slightly impure products.

Preparation of Oximes.—(i) The following is a typical example. Cortisone acetate (1 g.), dissolved in anhydrous pyridine (20 ml.), was mixed with a solution of hydroxylamine hydrochloride (1 g.) in anhydrous pyridine (10 ml.), and the solution set aside at room temperature. The α (1 dm. tube) +7·83° changed to +6·70° in *ca.* 64 hr. and did not change thereafter. Careful dilution with water then precipitated the dioxime (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = O$, $R^4 = Ac$) nearly quantitatively. For further details of this and related preparations, see Table 2.

Such products were generally pure. Attempts at crystallisation may lead to decomposition.

The oxime methyl ethers were made similarly. Dioximation of the 21-alcohols was complete within 24 hr.

(ii) Substance S (0·56 g.) in methanol (12 ml.) and methylene dichloride (6 ml.) was treated with a filtered mixture of hydroxylamine hydrochloride (0·472 g.) and 0·339N-sodium methoxide in methanol (24 ml.). The alkaline solution was set aside at room temperature for a weekend. Subsequent acidification with acetic acid and dilution with water precipitated the dioxime (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = H_2$, $R^4 = H$) (0·48 g.), with a second crop (0·07 g.), identified with the oxime so described in Table 2.

(iii) 4 : 5α-Dihydrocortisone acetate (0·5 g.) in ethanol (50 ml.) was treated with hydroxylamine hydrochloride (0·5 g.) and crystalline potassium acetate (0·9 g.), the two last being dissolved in ethanol (12·5 and 15 ml. respectively) and mixed just before use. The mixture was left at room temperature for 20 hr., and the oxime (I; $R^1 = N{\cdot}OH$, $R^2 = R^3 = O$, $R^4 = Ac$) isolated by extraction into ether or methylene dichloride or by precipitation with water. This product (0·49 g.) was crystallised from ethyl acetate to give a pure specimen (0·30 g.) (see Table 2).

This method did not give pure 20-oximes from the 21-acetates, since forcing conditions produced mixtures. 20-Oximation in this manner of the 21-alcohols was very slow.

The oximes listed in Table 2 were made by method (i) with a few exceptions (see footnote) or by selective hydrolysis (see below). A blank in the yield column denotes preparation by hydrolysis or, in the case of a derivative, by acylation. The yields are for material purified by precipitation from aqueous pyridine until it gave only one spot on a paper chromatogram.

The following oximes, not mentioned in Table 2, were made by the methods mentioned above: (+)-Camphor oxime (methods i and iii), m. p. 117—118° (cap.), $[\alpha]_D$ −41° (in EtOH) {lit.,[39] m. p. 119°, $[\alpha]_D$ −42° (in EtOH)}. 4-Hydroxyimino-2-methylpent-2-ene (from mesityl oxide by method iii), b. p. 92—94°/15 mm., $\lambda_{max.}$ 233 mμ (ε 8760) (lit.,[40] b. p. 95°/11 mm. for

[38] Cf. Slates and Wendler, *J. Org. Chem.*, 1957, **22**, 498.
[39] " Dictionary of Organic Compounds," ed. Heilbron and Bunbury, Eyre and Spottiswood, London, 1943, Vol. I, p. 384.
[40] *Op. cit.*, 1936, Vol. II, p. 593.

TABLE 2. *Properties of the oximes.*

No.	Compound	Yield (%)	Cryst. habit (solvent)	M. p.	$[\alpha]_D$	$\lambda_{max.}$ (mμ)	ε
Substance S							
1	3 : 20-Dioxime	95	Prisms (MeOH)	225—227°	+123°	241	19,200
2*a*	3 : 20-Dioxime Me_2 ether	87	(i) Needles (Aq. $COMe_2$) [a,b]	164, 180	+167	249	17,600
2*b*			(ii) Plates ($COMe_2$) [b]	194—196	+132	249	23,000
Substance S 21-acetate							
3	3 : 20-Dioxime	88	Needles (Aq. MeOH)	174—176	+136	240	21,400
Substance D 3 : 21-diacetate							
4	20-Oxime	100	Nacreous (EtOAc)	231—232	+13	—	—
5	20-Oxime acetate [c]	—	Needles (Aq. $COMe_2$)	176—178	+23	—	—
4 : 5α-Dihydrocortisone 21-acetate							
6	3-Oxime [d]	95	Prisms (EtOAc)	276—279	+97	—	—
7	3 : 20-Dioxime	89	Needles (EtOAc)	203—204	+41	—	—
Cortisone							
8	3-Oxime	—	Needles (Aq. EtOH)	149—150	+220	240	18,400
9	3 : 20-Dioxime [c]	91	Needles (Aq. $COMe_2$)	200	+167	240	20,700
Cortisone 21-acetate							
10	3-Oxime [d]	91	Needles (Aq. EtOH)	250—252	+235	240	20,400
11	3 : 20-Dioxime	98	Needles (EtOAc–CH_2Cl_2–hexane) [e,f]	207—209	+162	240	22,600
12	3 : 20-Dioxime Me_2 ether	85	Needles (Aq. EtOH) [b]	159·5—162·5	+203	249	20,200
Cortisone, 3-ethylene ketal [c]							
13	20-Oxime	91	Needles (MeOH)	233—234	−2	—	—
Cortisone 21-acetate, 3-ethylene ketal							
14	20-Oxime	69	Prisms (Aq. EtOH)	218—223	+9	—	—
Cortisol							
15	3-Oxime [e]	—	Needles (Aq. $COMe_2$)	146—148, 190	+121	240	18,500
16	3 : 20-Dioxime [e]	83	Needles (Aq. MeOH)	205—207	+125	240	22,700
17	3 : 20-Dioxime Me_2 ether [e]	—	Crystals (EtOAc–*cyclo*hexane)	78—83	+167	249	30,000
Cortisol, 3-ethylene ketal							
18	20-Oxime	—	Rods (Aq. $COMe_2$)	231—234	−37	—	—

		Found (%)			Required (%)		
No.	Formula	C	H	N	C	H	N
1	$C_{21}H_{32}O_4N_2$	66·7	8·6	7·3	67·0	8·6	7·4
2*a*	$C_{23}H_{36}O_4N_2$	67·7	8·8	7·1	68·3	9·0	6·9
2*b*	$C_{23}H_{36}O_4N_2$	68·35	8·7	7·1	68·3	9·0	6·9
3	$C_{23}H_{34}O_4N_2$	65·4	7·9	6·5	66·0	8·2	6·7
4	$C_{25}H_{37}O_7N$	64·8	8·0	3·1	64·8	8·05	3·0
5	$C_{27}H_{39}O_8N$	64·7	7·6	2·8	64·2	7·8	2·8
6	$C_{23}H_{33}O_4N$	65·8	7·9	3·2	65·85	7·9	3·3
7	$C_{23}H_{34}O_4N_2$	63·9	7·75	5·8	63·6	7·9	6·45
8	$C_{21}H_{29}O_5N,H_2O$	64·0	7·6	3·0	64·1	7·9	3·6
9	$C_{21}H_{30}O_5N_2,H_2O$	61·95	7·9	6·7	61·7	7·9	6·9
10	$C_{23}H_{31}O_4N$	66·4	7·3	3·5	66·2	7·5	3·4
11	$C_{23}H_{32}O_6N_2$	63·9	7·1	6·7	63·9	7·4	6·5
12	$C_{25}H_{36}O_6N_2$	65·5	8·05	6·5	65·2	7·9	6·1
13	$C_{23}H_{33}O_4N$	65·6	7·7	3·4	65·9	7·9	3·3
14	$C_{25}H_{39}O_7N$	65·25	7·8	3·3	65·05	7·6	3·0
15	$C_{21}H_{31}O_5N,0·5H_2O$	65·4	8·1	3·5	65·3	8·3	3·6
16	$C_{21}H_{32}O_5N_2,H_2O$	61·7	8·2	7·0	61·4	8·35	6·8
17	$C_{23}H_{36}O_5N_2,2C_6H_{12}$	70·6	9·6	4·6	71·4	10·3	4·8
18	$C_{23}H_{35}O_4N$	65·4	8·5	3·4	65·5	8·4	3·3

[a] Double m. p. [b] α_D for $CHCl_3$ solution. [c] For further information, see below. [d] Made by method (iii). [e] M. p. variable. [f] For published data on this compound, see ref. 4.

"β"-form). 2-Hydroxyimino-3 : 3-dimethylbutane (from pinacolone by method iii), m. p. 74—77° (capillary) (Found: N, 10·4. Calc. for $C_6H_{13}ON,H_2O$: N, 10·5%) (lit.,[41] m. p. 74—75°). *12-Hydroxyiminoligogenin acetate* (from hecogenin acetate by methods i and iii), laminæ (from ethyl acetate), m. p. 303—310° (decomp.), $[\alpha]_D$ +0·5° (in $CHCl_3$) (Found: C, 70·9; H, 8·95; N, 3·0. $C_{29}H_{43}O_5N$ requires C, 71·4; H, 9·3; N, 2·9%).

3β : 21-Diacetoxy-20-acetoxyimino-17α-hydroxy-5α-pregnan-11-one (III; R = N·OAc).—The 20-oxime (III; R = N·OH) (0·25 g.) of substance D 3 : 21-diacetate was heated on the water-bath for 5 min. with acetic anhydride (3 ml.) and pyridine (2 ml.). Evaporation with subsequent crystallisation from methanol of the dry residue gave needles of the *oxime acetate* (0·25 g., 92%) with the properties set out in Table 2.

Attempts at acetylating the 3 : 20-dioxime (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = O$, $R^4 = H$) likewise or with acetic anhydride and acetic acid, gave mixtures with up to four components detectable by paper chromatography.

Cortisone 3 : 20-Dioxime (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = O$, $R^4 = H$).—The 21-acetate (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = O$, $R^4 = Ac$) (1·0 g.) was suspended in methylene dichloride (20 ml.) under nitrogen, and 0·04N-sodium hydroxide in ethanol (27·3 ml., 1·0 mol.) added. Dioxan (22 ml.) and water (5 ml.) were run in, and the solution stirred for 10 min., and then neutralised (Congo-red) with acetic acid. Evaporation and washing of the product left a dried steroidal residue (0·89 g.), crystallising from aqueous acetone as needles (0·84 g., 89%), m. p. 198—203° (decomp.), identified with those obtained by direct oximation of cortisone (see Table 2).

Hydrolysis by means of water (1 mol.) in methanolic sodium methoxide was a little less efficient.[42]

Cortisol 3 : 20-Dioxime (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = H$, β-OH, $R^4 = H$).—(i) Cortisol (5·0 g.) in anhydrous pyridine (30 ml.) was treated with a solution of hydroxylamine hydrochloride (5·0 g.) in dry pyridine (50 ml.). The solution was kept at room temperature for 24 hr., evaporated to small bulk, and diluted with 50% aqueous methanol. The gum that separated was isolated by decanting the supernatant fluid; it was triturated with aqueous acetone to yield a white solid (4·47 g., 83%), m. p. 184—186° (decomp.), $\lambda_{max.}$ 239 mμ ($E^{1\%}_{1\,cm.}$ 499) (Found: N, 7·0%). It was purified by dissolving it in methanolic sodium methoxide (2 mol.), setting the solution aside overnight at 0°, and precipitating the sodium salt by addition of benzene. This gave a white gelatinous solid, m. p. 174—175°, that was washed with light petroleum (b. p. 40—60°). Treatment of this salt in aqueous suspension with carbon dioxide gave a precipitate, m. p. 202—205° (decomp.), $[\alpha]_D$ +125°, characterised (after crystallisation from aqueous methanol) by the properties set out in Table 2.

(ii) Cortisone 3 : 20-dioxime (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = O$, $R^4 = H$) (1·0 g.) was reduced with lithium borohydride according to the instructions given by Wendler *et al.*[2, 15] The water-washed product (0·87 g.) was got as rhombs, m. p. >330°, becoming brown at >240°. Precipitation from methanol gave a purer solid (0·53 g.), m. p. >310°, $[\alpha]_D$ +154° (*c* 0·58; acetic acid), $\lambda_{max.}$ 241 mμ ($E^{1\%}_{1\,cm.}$ 414), devoid of carbonyl absorption in its infrared spectrum (Found: B, 4·1%) (Graber and Wendler [15] isolated a compound with similar m. p., $[\alpha]_D$, and ultraviolet absorption, and called it the 3 : 20-dioxime of cortisol).

The foregoing boron-containing compound (0·28 g.) was heated in refluxing methanol until the vapour over the solution no longer burnt with a green-edged flame (*ca.* 5 hr.). Evaporation of the solvent left a residue (0·28 g.), sintering at *ca.* 123°, and fusing to a varnish at *ca.* 180°. Two crystallisations from ethyl acetate–*n*-hexane afforded a fine powder (0·22 g.), shrinking at 158—162°, m. p. 171—177° (capillary) (to a varnish), decomp. >213°, of the *dioxime* (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = H$, β-OH, $R^4 = H$) (Found: C, 63·8; H, 8·5; N, 6·7. $C_{21}H_{32}O_5N_2$ requires C, 64·3; H, 8·2; N, 7·1%). Crystallisation from aqueous methanol gave a hydrate, m. p. 199° (decomp.), $[\alpha]_D$ +123°, $\lambda_{max.}$ 240·5 mμ (ε 19,800), identified with the compound described in Table 2.

[The action of lithium borohydride in anhydrous solvents on the 3 : 20-dioxime (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = H_2$, $R^4 = H$) of substance S produced an infusible compound, from which the original dioxime was regenerated by refluxing methanol. Sodium borohydride in methanol at 20° or refluxing did not change this dioxime; it was also stable in aqueous alcoholic

[41] *Op. cit.*, 1937, Vol. III, p. 493.
[42] Huang-Minlon and Tishler, U.S.P. 2,634,277.

alkali. The dioxime and boric acid in refluxing aqueous tetrahydrofuran did not yield a boron-containing steroid.]

Cortisol **3 : 20-*Dioxime Dimethyl Ether*** (II; $R^1 = R^3 = N{\cdot}OMe$, $R^2 = H$, β-OH, $R^4 = H$).—The 3 : 20-dioxime dimethyl ether of cortisone acetate (II; $R^1 = R^3 = N{\cdot}OMe$, $R^2 = O$, $R^4 = Ac$) (1·27 g.) in ethanol (20 ml.) containing N-sodium hydroxide (2·75 ml.) was treated with sodium borohydride (0·6 g.) in water (0·5 ml.), the cloudy mixture then being refluxed for 4 hr. More borohydride (0·6 g.) in water (0·5 ml.) was added, and the refluxing continued for another 2 hr. Neutralisation of the cooled mixture with 10% (v/v) aqueous acetic acid and extraction with methylene dichloride yielded a steroid (1·03 g.) almost devoid of infrared carbonyl absorption. This steroid was heated in refluxing methanol (25 ml.) for 4 hr., after which the vapours no longer burnt with a green flame. The boron-free residue left after evaporation was still almost devoid of carbonyl absorption, and crystallised to give the non-ketonic dioxime dimethyl ether (0·32 g., 20%). Its properties (Table 2) suggest that it is a clathrate compound.[43]

Substance S **20-*Nitrimine*** (IV; $R = H_2$).—The dioxime (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = H_2$, $R^4 = H$) (1·0 g.) was dissolved in acetic acid (25 ml.) containing crystalline potassium acetate (0·05 g.). 15% Aqueous sodium nitrite (5 ml.) was added, and then more if the starch–iodide test had become negative. Aliquot portions taken during 3 hr. showed that the nitrogen content of the steroid never dwindled to <6·5%. Precipitation with water then yielded the *nitrimine* which, crystallised from acetic acid, had m. p. 186—187°, $[\alpha]_D$ +80°, $\lambda_{max.}$ 240 mμ (ε 18,000) (0·68 g., 74%) (Found: C, 64·8; H, 7·8; N, 7·1. $C_{21}H_{30}O_5N_2$ requires C, 64·6; H, 7·7; N, 7·2%).

Cortisol **20-*Nitrimine*** (IV; R = H, β-OH).—Cortisol dioxime (0·95 g.) in acetic acid (30 ml.) was treated at room temperature with 5% aqueous sodium nitrite (20 ml.). The solution was set aside for 2 hr. during which a bright yellow colour developed rapidly and faded slowly. Dilution with aqueous sodium acetate precipitated a white solid (0·8 g., 71%), crystallisation of which from aqueous acetic acid yielded the *nitrimine* (0·40 g., 35%), m. p. 166—168° (decomp.), $[\alpha]_D^{24}$ +98°, $\lambda_{max.}$ 240 mμ (ε 17,200) (Found: C, 61·1; H, 7·3; N, 7·1. $C_{21}H_{30}O_6N_2,0{\cdot}5H_2O$ requires C, 60·8; H, 7·5; N, 6·8%).

3 : 3-*Ethylenedioxy*-17α : 21-*dihydroxy*-20-*nitriminopregn*-5-*en*-11-*one* (V; $R^1 = O$, $R^2 = N_2O_2$, $R^3 = H$).—The oxime (V; $R^1 = O$, $R^2 = N{\cdot}OH$, $R^3 = H$) (0·25 g.) in acetic acid (5 ml.) was treated with 5% aqueous sodium nitrite (5 ml.) for 4 hr., during which there separated irregular crystals of the *nitrimine* (V) (0·058 g.), m. p. 176—179° (decomp.) (Found: N, 6·2. $C_{22}H_{32}O_7N_2$ requires N, 6·25%).

The oxime acetate (III; R = N·OAc) and oxime methyl ethers were stable in such nitrosating conditions.

The 21-acetoxy-17α-hydroxy-20-oximes did not yield pure 20-nitrimines, owing to ready hydrolysis. The apparent thermal decomposition of an impure specimen of the 20-nitrimine of cortisone acetate could be attributed to hydration of the crystals. Attempts at acetylating the 21-hydroxy-20-nitrimines led to blackening.

12-*Nitriminotigogenin Acetate* (VI; $R = N_2O_2$).—The oxime (VI; R = N·OH) (0·50 g.) in pure dioxan (30 ml.) and acetic acid (5 ml.) was treated with a solution of sodium nitrite (1 g.) in water (5 ml.). A precipitate separated almost at once, but redissolved in 5 hr. Isolation of the product (0·53 g.), m. p. 185—187° (decomp.; capillary), by dilution with water and subsequent crystallisation from ethanol gave prisms of the *nitrimine* (VI; $R = N_2O_2$) (0·383 g.), m. p. 189° (decomp.), $[\alpha]_D$ +4° (in $CHCl_3$) (Found: C, 68·1; H, 8·8; N, 5·2. $C_{29}H_{44}O_6N_2$ requires C, 67·4; H, 8·6; N, 5·4%).

(+)-*Camphor Nitrimine.*—(+)-Camphor oxime (1·0 g.) in acetic acid (30 ml.) was treated with 5% aqueous sodium nitrite (15 ml.). A bright yellow colour developed and dispersed slowly, and the $[\alpha]_D$ (no correction for alterations in mol. wt.) rose from −50° to −43° in 0·5 hr.; thereafter it was constant. After another 1·5 hr. the product (0·90 g., 77%), m. p. 34—36° (capillary), was precipitated by the addition of water. Crystallisation from ethanol yielded the pure nitrimine (0·447 g.), m. p. 41—43° (capillary), $[\alpha]_D$ −32° (lit.,[44] m. p. 43°).

4-*Methyl*-2-*nitriminopent*-3-*ene.*—The oxime of mesityl oxide (5·0 g.) in acetic acid (7·5 ml.) was treated with pentyl nitrite (7·3 ml.). A vigorous reaction ensued and crystals were deposited. These were collected, washed with ethanol, and dried (3·81 g.; m. p. 138°). Three

[43] Cf. Baker, Gilbert, and Ollis, *J.*, 1952, 1443; Newman and Powell, *ibid.*, p. 3747.
[44] Angeli and Rimini, *Ber.*, 1895, **28**, 1078; *Gazzetta*, 1899, **29**, 36.

XUM

crystallisations from ethanol yielded a specimen of constant m. p. 136° (decomp.), 137—138° (capillary), $\lambda_{max.}$ 212·5 (ε 8910) and 310 mμ (ε 4460) (Found: C, 50·9; H, 7·1; N, 19·6. Calc. for $C_6H_{10}O_2N_2$: C, 50·7; H, 7·1; N, 19·7%) (lit.,[45] m. p. 155—156°). The infrared absorption of this compound lacked the usual bands attributed to the nitrimine system in the foregoing compounds but presented a powerful new maximum at 1480 cm.$^{-1}$.

Decomposition of Nitrimines.—(i) Cortisol nitrimine (IV; R = H, β-OH) (0·46 g.) was heated in dioxan (10 ml.) and water (10 ml.) for 5 hr. on the steam-bath, then evaporated under reduced pressure to small bulk. Methanol (20 ml.) was added, and evaporation under reduced pressure again carried out until precipitation began. Water was added; a product (0·30 g., 73%), m. p. 202—208°, $[\alpha]_D$ +149° (in dioxan), crystallised. Recrystallisation from methanol yielded cortisol as rhombs, m. p. 207—210°, $[\alpha]_D$ +164° (in MeOH), +154°, $\lambda_{max.}$ 241 mμ (ε 16,700) {lit.,[46] m. p. 215·5—221°, $[\alpha]_D^{24}$ +163° (in MeOH), $\lambda_{max.}$ 242 mμ (ε 16,100 in MeOH)}.

(ii) The nitrimine (IV; R = H_2) (0·16 g.) of substance S was decomposed similarly in dioxan (5 ml.) and water (5 ml.). The product, m. p. 197—205°, $[\alpha]_D$ +120° (in dioxan), $\lambda_{max.}$ 240·5 mμ (ε 16,000), was identified with substance S made by hydrolysis of its 21-acetate {lit.,[47] m. p. 202—213°, $[\alpha]_D^{23}$ +132°, $\lambda_{max.}$ 240 mμ (ε 16,600)}.

Similar decompositions could also be brought about with ethanol or acetonitrile containing water. No decomposition occurred in anhydrous solvents or on heating. The nitrimine derived from cortisone acetate (see below) contained water of crystallisation; when heated it melted, losing water, solidified, and finally melted as pure cortisone acetate. Attempts at acetylating the 21-hydroxy-20-nitrimines gave tars.

(iii) The nitrimine (VI; R = N_2O_2) (0·20 g.) derived from hecogenin acetate was heated for 1 hr. in refluxing dioxan (4·5 ml.) and water (1·5 ml.) containing urea (23·5 mg.). Crystals separated early and were isolated after dilution with water. This product (0·171 g., 93%), m. p. 243—249° (capillary), $[\alpha]_D$ −3° (in $CHCl_3$), was hecogenin acetate (VI; R = O) {lit.,[48] m. p. 245°, $[\alpha]_D^{25}$ −1° (in $CHCl_3$)}.

(iv) Camphor nitrimine (0·50 g.) was heated at 100° with water (5 ml.) containing urea (0·77 g.) in a Carius tube. The top of the tube was not heated, so that a sublimate (0·096 g.), m. p. 158—160°, collected where it could be easily removed. The infrared spectrum of this specimen was almost indistinguishable from that of pure camphor. It was resublimed at 150—160°/76 cm., giving a pure specimen, m. p. 174—175° (capillary).

(v) The nitrimine (0·50 g.) derived from mesityl oxide was heated with water (5 ml.) at 100° in a Carius tube for 24 hr. The subliming crystals (0·21 g.), m. p. 150—154°, were combined with material (0·16 g.), m. p. 149—150°, isolated by extraction with ether, and crystallised twice from chloroform, to give a product (0·12 g.), m. p. 150—153° (with a phase change at 125°), 155° (capillary), $\lambda_{max.}$ 262·5 mμ ($E_{1\,cm.}^{1\%}$ 595), $\nu_{max.}$ (Nujol) 1650 and 3250 cm.$^{-1}$ (Found: C, 50·8; H, 7·0; N, 18·9. Calc. for $C_6H_{10}O_2N_2$: C, 50·7; H, 7·1; N, 19·7%). This appears to be the compound described by Harries [45] with m. p. 156—157°, arising by the action of water at 120° on the nitrimine. We thank Mr. K. Bowden for doing this experiment.

Other Reactions with Nitrous Acid.—(i) To the 20-oxime (III; R = N·OH) (0·25 g.) of substance D 3 : 21-diacetate in acetic acid (8 ml.), 5% sodium nitrite (4 ml.) was added. The solution was left for 2 hr. at room temperature, then diluted with water and filtered. The washed and dried precipitate (0·22 g.), m. p. 180—195°, gave a weak test with TSTZ, and bands at 1310 and 1580 cm.$^{-1}$ in its infrared spectrum showed that it contained much nitrimine (Found: N, 4·2%). It was treated with refluxing 50% aqueous dioxan for 2 hr.; isolation then yielded the diacetate (III; R = O) (0·15 g., 62%), m. p. 215—220°, $[\alpha]_D$ +68°.

(ii) The dioxime (II; R^1 = R^3 = N·OH, R^2 = O, R^4 = Ac) (3 g.) of cortisone acetate in acetic acid (60 ml.) was treated during 10 min. with 5% sodium nitrite solution (60 ml.). The solution became yellow at first and evolved a colourless gas (probably nitrous oxide), but after 20 min. it was colourless and still. During the ensuing 100 min. crystals separated. Water precipitated a first crop (1·98 g.), $[\alpha]_D$ +156°, $\lambda_{max.}$ 237 mμ ($E_{1\,cm.}^{1\%}$ 358), melting at 125—140° with gas evolution, solidifying, and remelting at 218—223°, with $\nu_{max.}$ 1566 and 1305 cm.$^{-1}$;

[45] Harries and Gley, *Ber.*, 1899, **32**, 1330; Harries, *Annalen*, 1901, **319**, 230.
[46] Ref. 30; Wendler, Graber, Jones, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 3630.
[47] Ref. 30; Dorfman, *Chem. Rev.*, 1953, **53**, 47; Meystre, Vischer, and Wettstein, *Helv. Chim. Acta*, 1954, **37**, 1549.
[48] Wall, Krider, Rothman, and Eddy, *J. Biol. Chem.*, 1952, **198**, 533; cf. Sannié and Lapin, *Bull. Soc. chim. France*, 1952, 1080.

it gave a weak test with TSTZ [Found: H_2O (K. Fischer) 4·5; N, 3·15%]. A second crop (0·50 g.), m. p. 220—225°, was crude cortisone acetate, purifiable by crystallisation from acetone.

Part (0·25 g.) of the first crop was heated on the water-bath in dioxan (5 ml.) for 1 hr. Water was then added until steroid began to separate. This product (0·18 g.), m. p. 228—235°, $[\alpha]_D$ +225° (in $CHCl_3$), $\lambda_{max.}$ 237 mμ (ε 15,300), was cortisone acetate, the total corrected recovery of which was 69%.

(iii) The 3-oxime (II; R^1 = N·OH, R^2 = R^3 = O, R^4 = Ac) (0·10 g.) was treated in acetic acid (3 ml.) with 5% aqueous sodium nitrite (1 ml.). The solution darkened immediately, then became yellow after 3 min., a colourless gas being evolved. After a further 2 min., crystals (0·087 g., 90%), m. p. 222—232°, of cortisone acetate separated. Recrystallisation from acetone gave a purer specimen, m. p. 238—242°.

(iv) The dioxime (I; R^1 = R^3 = N·OH, R^2 = O, R^4 = Ac) (0·60 g.) of 4 : 5α-dihydrocortisone acetate was treated in the foregoing manner with acetic and nitrous acid. The solution, after an early green hue, became colourless. The product (0·34 g.) isolated after 2 hours' treatment melted at 160°, resolidified, and remelted at 195—198°. It gave a weak colour with TSTZ and its infrared spectrum included bands at 1580 and 1310 $cm.^{-1}$. Part (0·20 g.) was heated in refluxing dioxan (5 ml.) and water (5 ml.) for 90 min.; the cold solution deposited colourless plates (0·11 g., 33%), m. p. 233—237°, of 4 : 5α-dihydrocortisone 21-acetate.

Decompositions with Sulphurous Acid.—The dioxime (II; R^1 = R^3 = N·OH, R^2 = H_2, R^4 = H) (0·30 g.) of substance S in dioxan (10 ml.) was treated with a saturated aqueous solution of sulphur dioxide (10 ml.). The whole was heated on a steam-bath for 15 hr., sulphur dioxide being bubbled in all the time. Most of the solvent was evaporated and the residue diluted with water. Plates (0·197 g.), m. p. 180—200°, $[\alpha]_D$ +128°, separated; recrystallisation from aqueous ethanol gave pure substance S (0·14 g., 52%), m. p. 190—202°.

In a similar experiment in which sodium acetate was added as a buffer a more polar product was also detected. It was possibly the 3-oxime.

Partial Hydrolysis of 3 : 20-Dioximes.—(i) The dioxime (II; R^1 = R^3 = N·OH, R^2 = H_2, R^4 = H) (0·50 g.) of substance S was dissolved in warm 2N-hydrochloric acid (*ca.* 20 ml.) and set aside at room temperature for 2 days. Neutralisation of the solution and addition of water precipitated the 3-oxime (II; R^1 = N·OH, R^2 = H_2, R^3 = O, R = H), whose properties after crystallisation are given in Table 2.

(ii) After a similar experiment in which the dioxime (II; R^1 = R^3 = N·OH, R^2 = O, R^4 = H) (0·30 g.) of cortisone was stirred for 0·75 hr. with 2N-hydrochloric acid (30 ml.), the 3-oxime (II; R^1 = N·OH, R^2 = R^3 = O, R^4 = H) (0·261 g., 88%) was obtained (see Table 2).

(iii) Cortisol 3 : 20-dioxime (II; R^1 = R^3 = N·OH, R^2 = H, β-OH, R^4 = H) (0·50 g.) was hydrolysed in 0·75 hr. in solution in 2N-hydrochloric acid (25 ml.). The product (0·44 g., 89%), m. p. 145—150°, was mainly the 3-oxime (II; R^1 = N·OH, R^2 = H, β-OH, R^3 = O, R^4 = H), crystallisation of which gave the compound whose properties are given in Table 2.

Further Methods for Hydrolysing Oximes and their Methyl Ethers.—(i) The dioxime (II; R^1 = R^3 = N·OH, R^2 = H, β-OH, R^4 = H) (0·25 g.) of cortisol was dissolved in warm N-sulphuric acid (50 ml.) to which ammonium persulphate (0·16 g.) was added. Purified methylene dichloride (50 ml.) was added and the mixture shaken for 8 days at room temperature. A starch–iodide test on the aqueous phase was then still positive. Isolation of the steroid yielded cortisol (0·191 g.), crystallising from ethyl acetate with m. p. 205—208°, $[\alpha]_D$ +163° (*c* 1·64; MeOH), $\lambda_{max.}$ 242 mμ (ε 15,600). Ferric salts could not be used effectively instead of the persulphate.

With the following potential acceptors of the liberated hydroxylamine and in mild or vigorous conditions of acid hydrolysis the oxime groups were not removed or the reactions resulted in general destruction: pyruvic acid, acetone, benzaldehyde, 2 : 4-dinitrobenzaldehyde, furfural, chloral, and formaldehyde. With these acceptors catalysis by pyridine was also unsatisfactory. Pure products could not be isolated after the action of cupric acetate in acetic acid, Raney nickel in acetone, nitric acid in acetic acid, or selenium dioxide. Bromine in acetic acid failed to remove all the nitrogen, and *N*-bromosuccinimide in acetic acid, and *N*-bromoacetamide in dioxan containing perchloric acid, yielded substances containing nitrogen and bromine.

(ii) The dimethyl ether (II; R^1 = R^3 = N·OMe, R^2 = H, β-OH, R^4 = H) (75 mg.) of cortisol, mixed with 2N-hydrochloric acid (50 ml.), was shaken with methylene dichloride (50 ml.) for 5 days. A steroid (62 mg.) was then isolated and acetylated with acetic anhydride

(2 ml.) and pyridine (2 ml.) overnight at room temperature. The product was purified by chromatography over neutral alumina [49] to remove a less polar fraction (R_F 0·81) from the main fraction (R_F 0·50), which was cortisol 21-acetate, crystallising from acetone as rhombs (22 mg., 43%), m. p. 214—219°, $[\alpha]_D$ +158°. (Solvent N was used for the paper chromatography.)

21-*Acetoxy*-3 : 3-*ethylenedioxy*-17α-*hydroxypregn*-5-*ene*-11 : 20-*dione* (V; $R^1 = R^3 = O$; R^2 = Ac).—This compound was made in 97% yield from cortisone acetate with ethylene glycol refluxing at 20 mm. and toluene-*p*-sulphonic acid as catalyst.[1] The material so obtained, m. p. 272—280°, $[\alpha]_D^{22}$ +59° (in pyridine), was good enough for most purposes; crystallisation from aqueous pyridine gave a pure specimen, m. p. 286—288°, $[\alpha]_D$ +46° (in pyridine) (Found: C, 67·4; H, 7·6. Calc. for $C_{25}H_{34}O_7$: C, 67·3; H, 7·7%) {lit.,[50] m. p. 268—272°, $[\alpha]_D$ +49° (in pyridine)}.

The above acetate (5 g.) was suspended in methylene dichloride (200 ml.) and stirred under nitrogen. A solution of sodium hydroxide in methanol [made by adding 40% aqueous sodium hydroxide (5 ml.) to dry methanol (500 ml.); 0·114N; 98·0 ml., 1 mol.] was added in one lot. The steroid dissolved in 1·5 min., and stirring was continued for a total of 15 min.; the solution was then neutralised with acetic acid (phenolphthalein). Evaporation and subsequent dilution with water gave the crude 21-*hydroxy-ketal* (V; $R^1 = R^2 = O$, $R^3 = H$) (4·27 g., 94%, m. p. 191—198° (capillary). Crystallisation from ethyl acetate yielded prisms (3·2 g., 71%), m. p. 221—224°, $[\alpha]_D$ +32° (in pyridine). Further crystallisation gave the pure compound, m. p. 225—226°, $[\alpha]_D$ +32° (in pyridine) (Found: C, 68·2; H, 8·1. $C_{23}H_{32}O_6$ requires C, 68·3; H, 8·0%).

3 : 3-*Ethylenedioxy*-20-*hydroxyiminopregn*-5-*ene*-11β : 17α : 21-*triol* (V; R^1 = H, β-OH, R^2 = N·OH, R^3 = H).—The ketal oxime (V; R = O, R^2 = N·OH, R^3 = H) (0·50 g.) (see Table 2) in refluxing ethanol (11 ml.) was reduced in 3 hr. with sodium borohydride (0·40 g.) in water (2 ml.) and N-sodium hydroxide (5·2 ml.). Acidification with acetic acid and extraction with chloroform yielded an oxime (0·375 g., 75%), m. p. 200—204° (decomp.; capillary), which crystallised from aqueous acetone as rods (0·13 g., 61%) with the properties given in Table 2 for the ketal-oxime (V; R^1 = H, β-OH, R^2 = N·OH, R^3 = H).

The foregoing ketal oxime (0·371 g.) was dissolved in ethanol (40 ml.), and 2N-hydrochloric acid (40 ml.) was added. The $[\alpha]_D$ rose from +97° (3 min.) to +160° (22 hr.), at which it stayed constant. After 26 hr. the solution was neutralised with sodium hydrogen carbonate and extracted with chloroform, to yield a product (0·243 g.) which from ethyl acetate gave cortisol (0·105 g., 33%), m. p. 207—209° (decomp.), $[\alpha]_D$ +166° (in MeOH), $\lambda_{max.}$ 241 mμ (ε 15,300).

We thank Professor D. H. R. Barton, F.R.S., for discussions and comment and Johnson, Matthey and Co. Ltd., Wembley, Middlesex, for spectrographic analysis of the boron-containing compounds.

GLAXO LABORATORIES LTD.,
GREENFORD, MIDDLESEX.

[*Received, July 3rd,* 1958.]

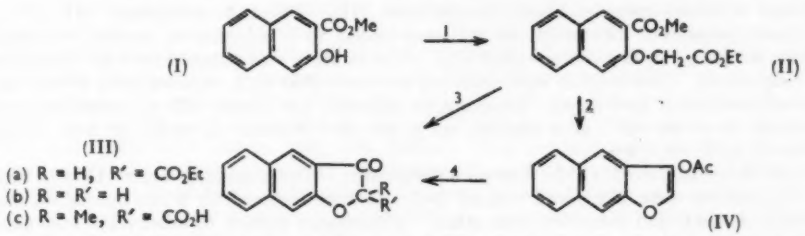
[49] Elks, Evans, Long, and Thomas, *J.*, 1954, 451.
[50] Sondheimer *et al.*, ref. 3.

931. *Naphtho(2′ : 3′-2 : 3)furan-4-one.*

By P. Emmott and R. Livingstone.

Naphtho(2′ : 3′-2 : 3)furan-4-one has been prepared by two methods from 2-hydroxy-3-naphthoic acid and a study made of its properties.

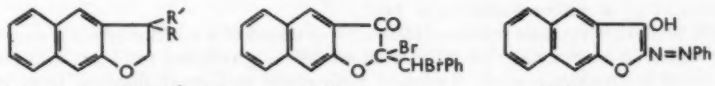
2 : 3-Naphthofuranones cannot be obtained by cyclisation of 2-naphthyl derivatives unsubstituted in the 1- and the 3-position;[1,2] they can, however, be prepared from suitable 2 : 3-disubstituted compounds. Methyl 3-hydroxy-2-naphthoate (I) was condensed with



Reagents: 1, Br·CH_2·CO_2Et–K_2CO_3. 2, NaOH; Ac_2O–NaOAc. 3, Na–C_6H_6; NaOH. 4, 2N-NaOH.

ethyl bromoacetate to give, after ring closure and hydrolysis, the furanone (IIIb) in a high overall yield. The conditions required for the hydrolysis of the ester (IIIa) were found to be critical. If the time of reaction was increased from ½ hr. to 3 hr., the product obtained was a high-melting orange solid, which was separated into a yellow solid insoluble in benzene, and a dark red solid soluble in benzene, neither of which could be obtained pure. The ester (IIIa) formed a sodio-derivative which condensed with methyl iodide. Hydrolysis of the product proceeded without decarboxylation and gave the acid (IIIc): ethyl 2-methyl-3-oxocoumaran-2-carboxylate was decarboxylated on hydrolysis, to afford 2-methylcoumaranone.[3]

Hydrolysis of the diester (II), followed by cyclisation with hot acetic anhydride and anhydrous sodium acetate, gave the acetate (IV). Hydrolysis with the calculated amount of 2N-sodium hydroxide solution afforded the furanone. The overall yield however was less than in the first method, mainly owing to the low yield of the acetate (IV).



(V): (a) R = Me, R′ = OH (b) R = R′ = Cl (VI) (VII)

Naphtho(2′ : 3′-2 : 3)furan-4-one (IIIb) with methylmagnesium iodide gave the alcohol (Va) which was readily dehydrated by formic acid to 4-methylnaphtho(2′ : 3′-2 : 3)furan. Treatment of the furanone (IIIb) with phosphorus pentachloride gave the dichloro-derivative (Vb) which readily lost hydrogen chloride to form 4-chloronaphtho(2′ : 3′-2 : 3)-furan. The existence of the methylene group was confirmed by the preparation of the benzylidene derivative, which was converted into the dibromide[4] (VI).

Treatment of the furanone with boiling potassium hydroxide solution for several hours afforded the same yellow and red products as were obtained from ethyl 4-oxonaphtho-(2′ : 3′-2 : 3)furan-5-carboxylate (IIIa).

[1] Ingham, Stephen, and Timpe, *J.*, 1931, 895.
[2] Stoermer and Bartsch, *Ber.*, 1900, **33**, 3176.
[3] Friedlander, *Ber.*, 1899, **32**, 1867.
[4] Auwers and Muller, *Ber.*, 1908, **41**, 4233.

Some evidence was found for the existence of the enolic modification of the furanone (IIIb), for boiling the compound with acetic anhydride gave 4-acetoxynaphtho(2′ : 3′-2 : 3)-furan (IV). Also a red dye, probably 4-hydroxy-5-phenyldiazonaphtho(2′ : 3′-2 : 3)furan (VII) was formed on treatment of the furanone (IIIb) with benzenediazonium chloride, a reaction typical of enolic and phenolic compounds.

The furanone (IIIb) was stable, no appreciable decomposition was observed on storage, and its reactions usually took place without the formation of resin.

Experimental

Ethyl 3-Methoxycarbonyl-2-naphthyloxyacetate (II).—Ethyl bromoacetate (12 c.c.) and anhydrous potassium carbonate (40 g.) were added to a solution of methyl 2-hydroxy-3-naphthoate (20 g.) in dry acetone (200 c.c.). The mixture was refluxed for 6 hr., then filtered, and evaporated. The residue was dissolved in ether (200 c.c.), washed with dilute sodium hydroxide solution, and dried. Evaporation afforded the *diester* (23 g.) which from light petroleum (b. p. 60—80°) gave needles, m. p. 60—61° (Found: C, 66·6; H, 5·8. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%).

Ethyl 4-Oxonaphtho(2′ : 3′-2 : 3)*furan-5-carboxylate*.—The foregoing ester (15 g.), benzene (70 c.c.), sodium dust (2 g.), and ethanol (0·2 c.c.) were refluxed for 3 hr., poured on ice and hydrochloric acid, and extracted with ether. The residue yielded to ether *ethyl 4-oxonaphtho*-(2′ : 3′-2 : 3)*furan-5-carboxylate* (12 g.), which from ethanol gave yellowish needles, m. p. 123° (Found: C, 70·2; H, 4·5. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%).

3-Carboxy-2-naphthyloxyacetic Acid.—The ester (II) (33 g.) was refluxed with 5% sodium hydroxide solution (600 c.c.) for 1 hr., poured over ice and dilute hydrochloric acid, and filtered. The product was treated with sodium hydrogen carbonate solution, filtered, and acidified. The precipitate was separated and crystallised from acetic acid, to afford the *diacid* (25 g.) as needles, m. p. 223—224° (Found: C, 62·9; H, 4·2. $C_{13}H_{10}O_5$ requires C, 63·4; H, 4·1%).

4-Acetoxynaphtho(2′ : 3′-2 : 3)*furan*.—3-Carboxy-2-naphthyloxyacetic acid (4 g.) was refluxed with acetic anhydride (100 c.c.) and anhydrous sodium acetate (8 g.) for 3 hr. and set aside overnight. The mixture was poured into water and set aside until the oil solidified. The product was filtered off and dissolved in ether. The ethereal solution was washed with sodium hydrogen carbonate solution and with water, dried, and evaporated to afford a solid (0·4 g.). Crystallisation from methanol (carbon) gave *4-acetoxynaphtho*(2′ : 3′-2 : 3)*furan* as needles, m. p. 78° (Found: C, 74·3; H, 4·4. $C_{14}H_{10}O_3$ requires C, 74·2; H, 4·4%).

Naphtho(2′ : 3′-2 : 3)*furan-4-one*.—(i) (*a*) Ethyl 4-oxonaphtho(2′ : 3′-2 : 3)furan-5-carboxylate (1 g.) and 17% hydrochloric acid (20 c.c.) were refluxed for 2 hr. The mixture was steam-distilled and the solid in the distillate crystallised from ethanol, to afford naphtho(2′ : 3′-2 : 3)-furan-4-one (0·1 g.) as yellow plates, m. p. 148°.

(*b*) 30% Sodium hydroxide solution (150 c.c.) was added to a solution of ethyl 4-oxonaphtho-(2′ : 3′-2 : 3)furan-5-carboxylate (10 g.) in ethanol (50 c.c.), refluxed for ½ hr., and poured over ice and dilute hydrochloric acid. Isolation with ether and crystallisation from ethanol or glacial acetic acid afforded *naphtho*(2′ : 3′-2 : 3)*furan-4-one* (7 g.) as yellow plates, m. p. 148° (Found: C, 77·8; H, 4·4. $C_{12}H_6O_2$ requires C, 78·2; H, 4·3%).

(ii) 4-Acetoxynaphtho(2′ : 3′-2 : 3)furan (0·2 g.) in ethanol (10 c.c.) at 0° was added to 10% sodium hydroxide solution (0·5 c.c.) at 0° and immediately acidified with 3N-hydrochloric acid (1 c.c.). The mixture was poured over ice and water, and the product crystallised from ethanol to give naphtho(2′ : 3′-2 : 3)furan-4-one (0·07 g.) as yellow plates, m. p. and mixed m. p. 148°.

The furanone gave no colour with neutral ferric chloride solution and did not decolorise bromine water. With Fehling's solution, blue-violet flakes separated. A deep blue-violet colour was obtained on dissolving the furanone in concentrated sulphuric acid; it became dark brown on warming. Potassium permanganate solution was decolorised slowly in the cold, instantly on warming.

The 2 : 4-dinitrophenylhydrazone formed red needles (from nitrobenzene), m. p. 262°.

4-Acetoxynaphtho(2′ : 3′-2 : 3)*furan*.—Naphtho(2′ : 3′-2 : 3)furan-4-one (0·2 g.) was refluxed with acetic anhydride (5 c.c.) for 2 hr. The solution was poured into water and set aside overnight. The light brown solid was separated and crystallised from methanol, to give 4-acetoxynaphtho(2′ : 3′-2 : 3)furan (0·2 g.), m. p. and mixed m. p. 78°.

XUM

4-*Hydroxy*-5-*phenyldiazonaphtho*(2′ : 3′-2 : 3)*furan*.—Aniline hydrochloride in dilute hydrochloric acid was added to a solution of sodium nitrite. The cold mixture was added to a suspension of naphtho(2′ : 3′-2 : 3)furan-4-one in dilute sodium hydroxide solution, and a bright red solid was immediately formed.

Action of Alkali on Ethyl 4-*Oxonaphtho*(2′ : 3′-2 : 3)*furan*-5-*carboxylate*.—25% Potassium hydroxide solution (20 c.c.) was added to a solution of ethyl 4-oxonaphtho(2′ : 3′-2 : 3)furan-5-carboxylate (1 g.) in ethanol (20 c.c.). The solution, with air passing through it, was refluxed for 4 hr., then filtered and poured over ice and dilute hydrochloric acid, to give a reddish-brown solid (0·7 g.). Extraction with benzene gave a yellow solid (0·1 g.), m. p. 220—230°, insoluble in benzene, and a red solid (0·1 g.), m. p. >250°, soluble in benzene.

5-*Methyl*-4-*oxonaphtho*(2′ : 3′-2 : 3)*furan*-5-*carboxylic Acid*.—Ethyl 4-oxonaphtho(2′ : 3′-2 : 3)furan-5-carboxylate (1 g.), dissolved in absolute alcohol (5 c.c.), was added to a solution from sodium (0·1 g.) in absolute alcohol (2 c.c.). Methyl iodide (0·4 c.c.) was added and the mixture refluxed for 3 hr. The ethanol was then evaporated, water added, and the product isolated with ether. On evaporation, ethyl 5-methyl-4-oxonaphtho(2′ : 3′-2 : 3)furan-5-carboxylate was obtained as a light brown gum (0·4 g.); this was dissolved in ethanol (7 c.c.), and refluxed with 20% sodium hydroxide solution (7 c.c.) for 1 hr. The mixture was poured over ice and dilute hydrochloric acid, and filtered. The product was treated with sodium hydrogen carbonate solution, and the whole filtered, and the filtrate was acidified. The precipitate recrystallised from dilute ethanol (carbon), to afford 5-*methyl*-4-*oxonaphtho*(2′ : 3′-2 : 3)*furan*-5-*carboxylic acid* as white spangles (0·07 g.), m. p. 206—207° (Found: C, 68·8; H, 4·3. $C_{14}H_{10}O_4$ requires C, 69·3; H, 4·1%).

4 : 5-*Dihydro*-4-*hydroxy*-4-*methylnaphtho*(2′ : 3′-2 : 3)*furan*.—A solution of naphtho(2′ : 3′-2 : 3)furan-4-one (1·8 g.) in dry ether (200 c.c.) was slowly added to a stirred solution of methylmagnesium iodide (2·6 g.) in dry ether (10 c.c.). The mixture was refluxed for 1 hr. and poured over ice and ammonium chloride solution. The product was isolated with ether as a yellow solid (1·9 g.). Crystallisation from light petroleum (b. p. 80—100°) gave 4 : 5-*dihydro*-4-*hydroxy*-4-*methylnaphtho*(2′ : 3′-2 : 3)*furan* as pale yellow needles, m. p. 113—114° (Found: C, 78·2; H, 5·9. $C_{13}H_{12}O_2$ requires C, 78·0; H, 6·0%).

4-*Methylnaphtho*(2′ : 3′-2 : 3)*furan*.—The preceding compound (0·16 g.) was refluxed for ½ hr. with formic acid (5 c.c.; *d* 1·2). Removal of the acid afforded a white solid (0·14 g.); addition of a saturated solution of picric acid and crystallisation from methanol gave red needles, m. p. 121—122° (Found: C, 55·7; H, 3·4; N, 10·4. $C_{19}H_{13}O_8N_3$ requires C, 55·6; H, 3·1; N, 10·2%). This *picrate* in ether was decomposed by chromatography, giving 4-*methylnaphtho*(2′ : 3′-2 : 3)*furan* as needles, m. p. 63° (Found: C, 85·2; H, 6·0. $C_{13}H_{10}O$ requires C, 85·6; H, 5·5%).

4-*Chloronaphtho*(2′ : 3′-2 : 3)*furan*.—Naphtho(2′ : 3′-2 : 3)furan-4-one (0·3 g.) was mixed with phosphorus pentachloride (3 g.) and set aside overnight in a vacuum-desiccator. The mixture was extracted with ether, and the ethereal solution treated with solid sodium carbonate. The whole was filtered and the filtrate evaporated. Isolation with ethanol (carbon) and crystallisation from methanol gave 4-*chloronaphtho*(2′ : 3′-2 : 3)*furan* (0·07 g.) as pale yellow plates, m. p. 81—82° (Found: C, 70·5; H, 3·7. $C_{12}H_7OCl$ requires C, 70·9; H, 3·4%).

5-*Benzylidenenaphtho*(2′ : 3′-2 : 3)*furan*-4-*one*.—10% Sodium hydroxide solution (0·6 c.c.) was added to a hot solution of naphtho(2′ : 3′-2 : 3)furan-4-one (0·5 g.) and benzaldehyde (0·4 g.) in ethanol (10 c.c.). After 1 min. a solid separated and was isolated. Crystallisation from ethanol afforded the 5-*benzylidene derivative* (0·7 g.) as yellow needles, m. p. 189—190° (Found: C, 83·7; H, 4·6. $C_{19}H_{12}O_2$ requires C, 83·8; H, 4·4%).

5-*Bromo*-5-α-*bromobenzylnaphtho*(2′ : 3′-2 : 3)*furan*-4-*one* (VI).—A solution of 5-benzylidenenaphtho(2′ : 3′-2 : 3)furan-4-one (0·3 g.) in chloroform (10 c.c.) was treated with bromine (0·07 c.c.) in chloroform (1 c.c.) and set aside for 24 hr. The chloroform was removed and the product crystallised from ethanol, to give the *dibromo-derivative* (0·4 g.) as yellow needles, m. p. 166—167° (Found: C, 52·5; H, 2·8. $C_{19}H_{12}O_2Br_2$ requires C, 52·7; H, 2·8%).

MUNICIPAL COLLEGE, BURNLEY. [*Received, July 4th*, 1958.]

XUM

932. *Properties and Reactions of Free Alkyl Radicals in Solution. Part XII.* Evidence for Radical-catalysis of Hydrogen Transfer.*

By R. A. Jackson and William A. Waters.

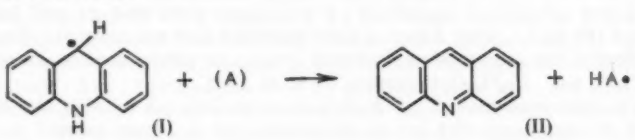
2-Cyano-2-propyl radicals attack acridan, giving acridine, di-9-acridanyl, and 9-(2-cyano-2-propyl)acridan. Mercaptoacetic acid promotes the reaction.

In the presence of 2-cyano-2-propyl radicals at 80—100° the conversion of acridan into acridine is effected by azobenzene, *m*-dinitrobenzene, and 1 : 3 : 5-trinitrobenzene; at this temperature there is little hydrogen transfer in the absence of the cyanopropyl radicals. Catalysed reduction of tetrazolium salts has also been noted.

Diphenylnitrogen radicals have only weak hydrogen-abstracting power.

2-Cyano-2-propyl and related radicals scarcely dehydrogenate aliphatic aldehydes (Part IV [1]) except in the presence of a thiol,[2] and in the absence of a thiol do not attack 9 : 10-dihydroanthracene.[3,4] We find, however, that acridan (9 : 10-dihydroacridine) is attacked by 2-cyano-2-propyl radicals giving, under optimum conditions, 14% of acridine, 27% of di-9-acridanyl, and 48% of 9-(2-cyano-2-propyl)acridan, the formation of the last two showing that radical dehydrogenation occurs at the *meso*-CH_2 group and not at >NH. Mercaptoacetic acid appreciably catalyses this dehydrogenation. 9-Phenylacridan is less easy to dehydrogenate, whereas diethyl 1 : 4-dihydrocollidine-3 : 5-dicarboxylate is not dehydrogenated even in the presence of mercaptoacetic acid.

In the presence of a hydrogen atom acceptor, such as azobenzene, *m*-dinitrobenzene, or 1 : 3 : 5-trinitrobenzene, much more hydrogen can be removed from acridan at temperatures that are far too low for appreciable direct hydrogen-transfer to the ultimate oxidant. Thus no reaction occurred when a solution of acridan and azobenzene in benzene was refluxed for 4 hours, but in presence of excess of αα′-azo*iso*butyronitrile 85% of the azobenzene was reduced. (2-Cyano-2-propyl radicals did not react directly with azobenzene.) When a solution of acridan and *m*-dinitrobenzene in benzene was refluxed for 8 hours, only 0·4% of acridine was produced, but on addition of αα′-azo*iso*butyronitrile 31% of acridine was formed, only 11% of which corresponds to the direct attack of 2-cyano-2-propyl radicals on the acridan. With 1 : 3 : 5-trinitrobenzene over a similar period there was only 4% of direct reaction, and a 64% conversion in the presence of 2-cyano-2-propyl radicals, corresponding to 49% of radical-catalysed hydrogen transfer. Colour tests with 2 : 3 : 5-triphenyltetrazolium chloride, and with 3 : 3′-dimethoxydiphenyl-4 : 4′-bis-(3 : 5-diphenyltetrazolium) dichloride (" blue tetrazolium salt ") have given further evidence of a radical-catalysed hydrogen transfer which can be promoted by the addition of mercaptoacetic acid, though the occurrence of side reactions has made it difficult to obtain quantitative data.



(I) (II)

It is thus evident that, when 2-cyano-2-propyl radicals have attacked acridan to give the 9-acridanyl radical (I), the latter can then transfer a hydrogen atom to a suitable acceptor

* Part XI, *J.*, 1958, 3221.

[1] Harris and Waters, *J.*, 1952, 3108.
[2] *Idem*, *Nature*, 1952, **170**, 212.
[3] Bickel and Kooyman, *ibid.*, p. 211.
[4] Beckwith and Waters, *J.*, 1957, 1001.

molecule (A), such as azobenzene or a polynitro-compound, the extra resonance energy of the anthracene-type ring system being available from the conversion of (I) into (II) to provide a driving force for the reaction.

Radiochemical evidence for homolytic hydrogen-transfer to certain heterocyclic molecules is now definite,[5] but attempts to set up radical chains:

$$HX\cdot + A \longrightarrow X + HA\cdot\ ;\quad HA\cdot + XH_2 \longrightarrow HX\cdot + H_2A$$

by the generation of semiquinone radicals [6] have failed, probably because in these selected systems at least one of the radicals concerned (HA· or HX·) has a resonance structure of too low energy content for attack on C–H bonds. Chain processes of this type occur, of course, in autoxidations where A is oxygen (O_2).

Chain dehydrogenation by the radical $(CH_2{\cdot}CO)_2N\cdot$, which has little resonance stabilisation, is undoubtedly involved in the homolytic reaction of *N*-bromosuccinimide. We have attempted to dehydrogenate other molecules with the diphenylnitrogen radical $Ph_2N\cdot$ and find that it will attack hydrazobenzene giving azobenzene, and 9 : 10-dihydroanthracene giving anthracene. It does not attack cumene, tetralin, or *cyclo*hexene. Here again, as with diphenylpicrylhydrazyl,[7] we have an inactive radical.

Experimental

Free-radical experiments were carried out under oxygen-free nitrogen. M. p.s are corrected.

Reaction of αα′-Azoisobutyronitrile with Acridan.—Acridan (5·0 g.) and αα′-azo*iso*butyronitrile (9·0 g.) in dry benzene (250 ml.) were refluxed for 7 hr. Colourless crystals of insoluble di-9-acridanyl, m. p. 252° (0·58 g., 12%), separated (Found: C, 86·9: H, 5·4; N, 7·4. Calc. for $C_{26}H_{20}O_2$: C, 86·6; H, 5·6; N, 7·8%) and were identified by conversion with sulphuric acid into 1 : 2-di-(*o*-anilinophenyl)ethylene oxide,[8] m. p. 165°. The solvent was removed from the remainder, which was then steam-distilled. The distillate was extracted with benzene, and the benzene solution was extracted with 2N-hydrochloric acid. On evaporation of the benzene solution, tetramethylsuccinonitrile (3·4 g.) was obtained, whilst the acid extracts, after neutralisation and extraction with ether, gave acridine (0·28 g.). The involatile residue was fractionally crystallised from benzene and light petroleum (60—80°), giving acridan, m. p. 169° (1·53 g., 30%), more acridine (0·73 g., total 20%) and 9-(2-*cyano*-2-*propyl*)*acridan* (1·1 g., 16%), m. p. 164° (decomp.) (Found: C, 82·4; H, 6·4; N, 11·6. $C_{17}H_{16}N_2$ requires C, 82·2; H, 6·5; N, 11·3%). The ultraviolet spectrum of this compound in alcohol resembled that of acridan, having $\varepsilon_{max.} = 1{\cdot}8 \times 10^4$ at 279 mμ whilst its infrared spectrum (Nujol mull) had absorption at 4·49 (·CN), 7·20 and 7·29 (·CMe_2), and 2·97 μ (NH).

By addition during 24 hr. of the azo-nitrile (3·6 g., 2 mol.) in benzene (100 ml.) to a refluxing solution of acridan (2·0 g., 1 mol.) in benzene (100 ml.), 0·54 g. (27%) of insoluble di-9-acridanyl was obtained. Spectroscopic analysis of the remaining solution indicated yields of 14% of acridine and 48% of 9-(2-cyano-2-propyl)acridan, with no remaining acridan.

To acridan (2·0 g.) and the azo-nitrile (3·6 g.) in boiling benzene (60 ml.), mercaptoacetic acid (0·36 g.) in benzene (40 ml.) was added in small portions during ½ hr. and heating was continued for a further 7 hr. From this mixture 9% of di-9-acridanyl, 12% of acridine, 5% of unchanged acridan, and 44% of 9-(2-cyano-2-propyl)acridan were isolated, so that addition of the thiol had markedly increased the yield of the last compound and decreased the amount of unchanged acridan.

Reaction of αα′-Azoisobutyronitrile with 9-Phenylacridan.—A solution of 9-phenylacridan [9] (0·42 g.) in benzene (250 ml.) was prepared. To 50 ml. (1 mol.) portions of this were added (*A*) αα′-azo*iso*butyronitrile (0·21 g., 4 mols.), (*B*) mercaptoacetic acid (0·03 g., 1 mol.), and (*C*) αα′-azo*iso*butyronitrile (0·21 g.) and mercaptoacetic acid (0·03 g.). The three solutions were refluxed for 8 hr. and then diluted to 100 ml. with benzene. Analysis of the ultraviolet spectra

[5] Stein and Swallow, *J.*, 1958, 306.
[6] Moore and Waters, *J.*, 1953, 3405.
[7] Braude, Brook, and Linstead, *J.*, 1954, 3574.
[8] Lehmstedt and Hundertmark, *Ber.*, 1930, **63**, 1229.
[9] Acheson, Hoult, and Barnard, *J.*, 1954, 4142.

of these solutions at 289, 355, and 385 mμ indicated that 9-phenylacridine had been produced in the following amounts: *A* 5%, *B* 11%, and *C* 22%.

Reaction of αα′-Azoisobutyronitrile with Diethyl 1 : 4-*Dihydrocollidine*-3 : 5-*dicarboxylate.*—A solution of diethyl 1 : 4-dihydrocollidine-3 : 5-dicarboxylate [10] (3·5 g.) and the azo-nitrile (4·3 g.) in benzene (100 ml.) was refluxed for 7½ hr. Tetramethylsuccinonitrile (2·8 g.) and unchanged dihydrocollidine ester (3·15 g., 90%) were recovered. Addition of mercaptoacetic acid (0·43 g.) to a similar mixture merely reduced the recovery of tetramethylsuccinonitrile to 2·38 g.; 2·44 g. were obtained in a control experiment without the ester.

Reaction of Acridan with Azobenzene in the Presence of αα′-Azoisobutyronitrile.—A solution of acridan (3·62 g., 2 mol.), azobenzene (1·82 g., 1 mol.), and αα′-azo*iso*butyronitrile (6·57 g., 4 mol.) in benzene (250 ml.) was refluxed for 4 hr. The solution was then still orange, with no appreciable precipitate, showing that the formation of di-9-acridanyl had been almost completely inhibited. The light absorption at 444 mμ of a sample, compared with that of a sample of the initial solution, showed that the azobenzene concentration was only 15% of its original value. The bulk of the product was recovered by evaporation and dissolved in ether, and the presence of hydrazobenzene was shown (*a*) by the intensification of the absorption at 444 mμ after oxidation with sodium hypobromite and (*b*) by the chromatographic isolation of a small quantity of benzidine after treatment with 6N-hydrochloric acid. The benzidine (m. p. 126—127°) was characterised by its mixed m. p. and infrared spectrum.

Control experiments showed that azobenzene did not react directly with acridan or αα′-azo-*iso*butyronitrile.

Reaction of Acridan with Nitro-compounds in the Presence of αα′-Azoisobutyronitrile.—A solution of 1 : 3 : 5-trinitrobenzene (0·85 g., 0·72 mol.), acridan (1·00 g., 1 mol.), and αα′-azo*iso*-butyronitrile (1·81 g., 2 mol.) in benzene was refluxed for 8 hr., cooled, and extracted with 2N-hydrochloric acid until the extracts were colourless. The hydrochloric acid solution was made alkaline with ammonia and extracted with ether, and the ethereal extracts were dried ($MgSO_4$) and made up to 250 ml. Half of this solution was evaporated and the residue was sublimed at 100° in a vacuum, giving acridine (0·318 g., 64%), m. p. 107—108°, characterised by its mixed m. p. and infrared spectrum.

Similar experiments were carried out with nitrobenzene and *m*-dinitrobenzene. In addition, control experiments without the azo-nitrile were conducted. In these experiments, acridine was estimated by its absorption at 250 mμ in ethanol solution. The results are shown in the Table.

Azonitrile (mol.)	Nitro-compound (mol.)	Acridine produced (%)	" Excess " of acridine (%)
2	Nil	11	—
2·2	Nitrobenzene (1 mol.)	14	3
Nil	*m*-Dinitrobenzene (1 mol.)	0·4	—
2	*m*-Dinitrobenzene (1 mol.)	31	20
Nil	1 : 3 : 5-Trinitrobenzene (0·72 mol.)	4	—
2	1 : 3 : 5-Trinitrobenzene (0·72 mol.)	64	49

1 mol. of acridan was used in each experiment.

Reaction of Acridan and Tetrazolium Chlorides in the Presence of αα′-Azoisobutyronitrile.—Decomposition of the azo-nitrile in water or ethanol does not produce reductive coloration of 2 : 3 : 5-triphenyltetrazolium chloride or of the analogous " blue tetrazolium salt." [11] Heating the tetrazolium salts in ethanol with acridan produces some colour, but much less than that in a mixture of all three components. With the " blue tetrazolium salt " the colour enhancement at 510 mμ due to the reduction of the salt was, with addition of the azo-nitrile, 27 times that without it.

Dehydrogenations with Diphenylnitrogen Radicals.—A solution of 9 : 10-dihydroanthracene (2·0 g.) and tetraphenylhydrazine (5·0 g.) in benzene (100 ml.) was refluxed for 4½ hr. After cooling, the solution was extracted with 6N-hydrochloric acid to remove diphenylamine (2·4 g.). The benzene was removed and the residue was separated chromatographically, giving anthracene, m. p. 213° (1·45 g., 73%), and unchanged 9 : 10-dihydroanthracene (0·47 g., 23%).

After refluxing for 4½ hr., a solution of hydrazobenzene (1 g.) and tetraphenylhydrazine

[10] Hantzsch, *Annalen*, 1882, **215**, 1.
[11] Haines and Waters, *J.*, 1955, 4256.

XUM

(2 g.) in benzene became deep orange. Spectroscopic analysis (visible absorption at 450 mμ) indicated 99% conversion into azobenzene; 87% of azobenzene, m. p. 67—68°, was recovered chromatographically.

Similar experiments with cumene, *cyclo*hexene, tetralin, and dimethyl succinate gave no evidence of hydrogen transfer.

One of us (R. A. J.) thanks the Department of Scientific and Industrial Research for a maintenance grant.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, July 17th*, 1958.]

---

933. *Electron Spin Resonance Spectra of the Carboxyhydroxymethyl Radical trapped after γ-Irradiation of Glycollic Acid.*

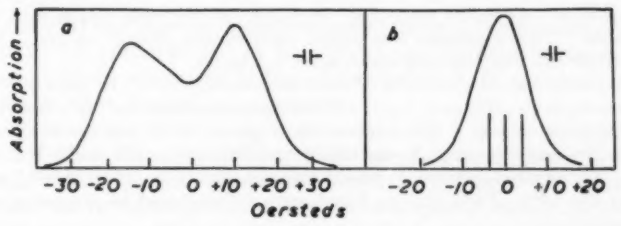
By P. M. GRANT, R. B. WARD, and D. H. WHIFFEN.

Electron resonance spectroscopy is used to identify the radical obtained on the irradiation of crystalline glycollic acid with gamma-rays as carboxyhydroxymethyl, HO·$\dot{C}$H·CO_2H.

HIGH-ENERGY radiation can break many molecules into free-radical fragments whose chemical nature has mostly been inferred from the isolation of stable end-products. If, however, the radicals can be trapped in a solid they themselves can be investigated by electron resonance spectroscopy and identified. *X*-Irradiated glycollic acid has previously [1] been thus investigated, but the conclusions were only tentative and are not in agreement with the present extended experimental findings.

Spectra.—γ-Irradiated polycrystalline glycollic acid showed two lines, 25 oersteds apart, of line-width $\Delta H_{m.s.}$ ~9 oersteds at room temperature. The central minimum occurred at a field appropriate to $g \sim 2$. Though of nearly equal intensity, the high-field component was slightly narrower and with a greater peak intensity as shown in the Figure, *a*. Some

Electron resonance spectra at 9200 Mc./sec., 3300 oersteds, centred on $g \sim 2$ for (a) γ-irradiated glycollic acid and (b) γ-irradiated [αα-$^2H_2$]glycollic acid. The vertical lines show expected splitting by the deuterium nuclear moment.



spectra showed signs of further structure with an additional, unresolved, weak feature just to the low-field side of the centre. This weak extra peak appeared to decay faster than the remainder of the spectrum and was absent from the other spectra described below; it is not considered significant. The signal was unchanged on opening the evacuated sample to air and was unchanged in intensity during three days but decayed to about 1/10th of the original intensity in six months. The spectrum was unchanged at 90° K but no irradiations at this temperature were undertaken. Calcium glycollate gave a very similar spectrum after irradiation though the lines were slightly closer (separation, 22 oersteds) and broader ($\Delta H_{m.s.}$ ~11 oersteds). [*carboxy*-$^2H_1$: *hydroxy*-$^2H_1$]Glycollic

[1] Gordy, Ard, and Shields, *Proc. Nat. Acad. Sci. U.S.A.*, 1955, **41**, 996.

acid, $DO{\cdot}CH_2{\cdot}CO_2D$, treated in the same way, gave the same spectrum as the protio-compound. In contrast, [$\alpha\alpha$-$^2H_2$]glycollic acid, $HO{\cdot}CD_2{\cdot}CO_2H$, gave a single-line spectrum (Figure, *b*) which was rather broad ($\Delta H_{m.s.}$ ~12 oersteds).

Discussion.—The two-peaked pattern of the Figure, *a*, shows [2] that there is one, and only one, hydrogen atom of spin ½ which couples strongly to the free electron. The persistence of this pattern in the calcium salt shows that it is not the acidic hydrogen atom. The hydroxylic hydrogen atom is eliminated because the *OO'*-dideutero-compound retains the pattern. The conclusion is inescapable that the hydrogen atom which couples was initially one of those on the CH_2 group, and this is confirmed by the disappearance of the two peaks when these atoms were replaced by deuterium. The spectrum predicted for the radical containing the C–D group would be three lines of equal intensity separated by only 6 oersteds. This is less than the line-width of each, ~9 oersteds, and a numerical synthesis of a derivative curve of this nature shows that the overlapping of lines is so strong that only one peak would be apparent if the individual lines had a width of ~9 oersteds and either Gaussian or Lorentzian shape. All the spectra show slight asymmetry with a sharper feature on the high-field side and this is tentatively ascribed to an anisotropic *g*-factor which can distort the line shape in polycrystalline materials.

These considerations show that one, and only one, of the central hydrogen atoms is lost in forming the stable radical. In the absence of measurements with ^{17}O- and ^{13}C-containing materials it cannot be proved that the remainder of the skeleton is unchanged, but there is no reason to suspect that it is not intact. The evidence thus strongly favours the structure $HO{\cdot}\dot{C}H{\cdot}CO_2H$ for the trapped radical. Apart from the very small inflection mentioned above, there is no indication of a second radical. One possible step is $\gamma + HO{\cdot}CH_2{\cdot}CO_2H \longrightarrow HO{\cdot}\dot{C}H{\cdot}CO_2H + H$, though this may occur in two separate stages, loss of an electron followed by a proton. If this were followed by $H + HO{\cdot}CH_2{\cdot}CO_2H \longrightarrow HO{\cdot}\dot{C}H{\cdot}CO_2H + H_2$ or $H + H \longrightarrow H_2$, no different radicals would be formed.

Experimental

The electron resonance spectra were measured at 9200 Mc./sec., 3300 oersteds, with 490 c./sec. modulation and with display of the derivative of the absorption on a pen recorder by use of the spectrometer described elsewhere.[3]

The compounds (50—150 mg.) were irradiated by a 200 c ^{60}Co γ-radiation source for 48 hr. in a sealed tube under high vacuum. The dose-rate was *ca.* $1{\cdot}5 \times 10^{18}$ ev g.$^{-1}$ min.$^{-1}$ and the radical yield *ca.* 2×10^{18} radicals/g.

Calcium Glycollate.—Glycollic acid (2 g.) in water (20 ml.) was neutralised with excess of calcium carbonate. The suspension was boiled, filtered, and allowed to cool. The crystalline salt was filtered off and recrystallised twice from hot water.

[carboxy-$^2H_1$: hydroxy-$^2H_1$]*Glycollic Acid.*—Deuterium oxide (10 ml., 99·78% D_2O) was distilled *in vacuo* on to glycollic acid (1 g.). The solution was kept for 1 hr., and then the solvent was removed by freeze-drying. This process was repeated with two further portions (10 ml.) of deuterium oxide, and the product was rapidly transferred to the irradiation tube in a dry-handling box. An infrared spectrum showed the material to be at least 90% exchanged and we believe that the 10% of OH groups found were reintroduced in preparing the sample for infrared spectroscopy.

[$\alpha\alpha$-$^2H_1$]*Glycollic Acid.*—" AnalaR " oxalic acid (10 g.) was dehydrated at 100° over phosphoric oxide *in vacuo*. The anhydrous oxalic acid was converted into the dideutero-form by freeze-drying it thrice from solution in deuterium oxide (10 ml., 99·78% D_2O) in a vacuum system. " AnalaR " sulphuric acid (1 ml.) was similarly converted into deuterium sulphate.

The anhydrous [$^2H_2$]oxalic acid and the deuterium sulphate were dissolved in deuterium oxide (10 ml., 99·78% D_2O) and transferred to a small electrophoresis cell in a dry-handling box. The solution was electrolysed at 60° with lead electrodes (12 v, 1 a, cathode area 25 cm.^{2}) by Ershov and Pyatnitskaya's method.[4]

[2] Wertz, *Chem. Rev.*, 1955, **55**, 829.
[3] Abraham, Ovenall, and Whiffen, *Trans. Faraday Soc.*, 1958, **54**, 1128.
[4] Ershov and Pyatnitskaya, *J. Chem. Ind.* (*U.S.S.R.*), 1941, **18**, No. 12, 13; *Chem. Abs.*, 1944, **38**, 3912.

XUM

The electrolysis was continued until, on cooling to room temperature, no oxalic acid crystallised. Further precautions to exclude moisture were unnecessary after this stage. The solution was adjusted to pH 7·5 with calcium hydroxide, stirred for 30 min., and neutralised with excess of carbon dioxide. The solution was boiled, filtered, and passed down a column of Zeo-Karb 225 (H^+ form). The acid eluate was then neutralised with excess of calcium carbonate, boiled, filtered, and concentrated. On cooling, the solution deposited crystals of crude calcium [$\alpha\alpha$-$^2H_2$]glycollate. This salt was recrystallised twice from hot water, and the free acid obtained by passing a solution of the salt down a column of Zeo-Karb 225 (H^+ form). The eluate was freeze-dried and sublimed twice *in vacuo* at 35° to yield the dideutero-acid (0·068 g.), m. p. 76°. The mixed m. p. with authentic glycollic acid was 77° (authentic glycollic acid has m. p. 79°). Its infrared spectrum was consistent with this structure with C–D stretching frequencies of the CD_2 group at 2169 and 2108 cm.$^{-1}$ and showed glycollic acid to be completely absent. Interpolation between the infrared spectra of glycollic acid (very strong band at 1090 cm.$^{-1}$) and [$\alpha\alpha$-$^2H_2$]glycollic acid (corresponding band at 1135 cm.$^{-1}$) suggests that [α-$^2H_1$]glycollic acid, $CHD(OH)\cdot CO_2H$, would probably absorb very strongly near 1112 cm.$^{-1}$; no such band was found in the product and its spectrum indicated it to be over 98% of the desired isotopic species.

We thank N. M. Atherton and B. P. Goddard for assistance with the spectral measurements and the United Kingdom Atomic Energy Authority, Research Group, Harwell for support and for maintenance grants (to P. M. G. and R. B. W.). We thank Professor M. Stacey and Dr. S. A. Barker for their interest.

Birmingham University. [*Received, July 25th*, 1958.]

---

934. *Organic Peroxides. Part IX.*[1] *A Stereochemical Study of the Formation of Alkyl Hydroperoxides from Hydrogen Peroxide.*

By Alwyn G. Davies and R. Feld.

Several optically active alkyl hydroperoxides (II) have been prepared by the reaction of hydrogen peroxide with the corresponding active alcohols (I) or their derivatives (Ia). Reduction of the hydroperoxide (II) back to the alcohol (III) permits conclusions to be drawn about the stereochemistry of the primary reaction.

In Parts VI [2] and VIII [1] we reported a stereochemical study of the formation and reduction of 1-phenylethyl hydroperoxide and of 1-methyl-1-phenylpropyl hydroperoxide respectively. Similar methods, illustrated in the scheme below, have now been applied to the investigation of a number of other hydroperoxides.

By the reaction of hydrogen peroxide with optically active 1-phenylethyl ether, 1-phenylpropanol, 1-phenylbutanol, 1-2′-naphthylethanol, 3-methylhexan-3-ol, 4-chlorodiphenylmethanol, and 2-1′-naphthylbutan-2-ol and its hydrogen phthalate, the corresponding optically active hydroperoxides have been prepared and characterised by their triphenylmethyl and/or 9-xanthenyl derivatives. The hydroperoxides from the first five compounds have been configurationally related to the corresponding alcohol by reduction. These results, and our previous ones, are summarised in Table 1.

Column 2 records the ratio of the rotatory power of the alcohol (III) to that of the hydroperoxide (II) from which it was obtained on reduction; where a number of reductions have been carried out, a mean value of α_{III}/α_{II} is recorded, the individual values appearing in the Experimental section.

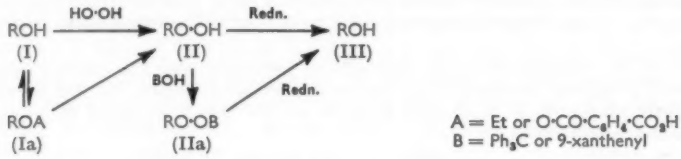
If we assume that the reduction proceeds without affecting the asymmetric centre of the molecule,[1,2] the factor in column 2 also represents in sign and magnitude the ratio of the

[1] Part VIII, Davies, *J.*, 1958, **3474**.
[2] Davies and Feld, *J.*, 1956, **665**.

rotations of the optically pure alcohol and hydroperoxide of like configuration. The maximum rotatory power of the alcohol (column 3) divided by this factor then gives an approximate value for the rotatory power of the optically pure hydroperoxide (column 4).

Column 5 records the percentage of activity remaining in the alcohol after the cycle alcohol (I) ⟶ hydroperoxide (II) ⟶ alcohol (III) (*i.e.*, $\alpha_{II}/\alpha_I \times \alpha_{III}/\alpha_{II}$). Again, the reduction (II) ⟶ (III) being assumed not to involve configurational change, this factor in column 5 represents in sign and magnitude the percentage configurational retention in the reaction (I) ⟶ (II). This factor will be minimal because no allowance has been made for the racemisation of the reactant or product.

When the reactant is a derivative of an alcohol (*i.e.*, ether or ester), the equivalent factor for the reaction is given by the expression $\alpha_{II}/\alpha_{Ia} \times \alpha_{Ia}/\alpha_I \times \alpha_{III}/\alpha_{II}$, where α_{Ia}/α_I is derived from an interconversion between (I) and (Ia) which proceeds with configurational retention.



In all the structural systems studied, the alcohol and its corresponding hydroperoxide and triphenylmethyl and 9-xanthenyl derivatives which have similar configurations have the same sign of rotation. The active hydroperoxides which we have prepared all have rotatory powers appreciably greater than those of the corresponding alcohols, but the reverse applies to Williams and Mosher's 1-methylhexyl hydroperoxide [3] and Ikeda's 1 : 2 : 3 : 4-tetrahydro-1-naphthyl hydroperoxide (Table). Both the magnitude and even the sign of rotation, however, may of course change as the solvent and wavelength are varied.

1 I or Ia	2 α_{III}/α_{II}	3 Max. α_{III}	4 Max. α_{II}	5 α_{III}/α_I (%)
Ph·CHMe·OH Ph·CHMe·OEt	+0·3$_0$ [a]	44·2° [b]	140° [a]	−3 [a] ≯−10
Ph·CHEt·OH	+0·2$_5$	27·8 [c]	120	−3
Ph·CHPr·OH	+0·5$_5$	51·4 [d, e]	95	+5
2-$C_{10}H_7$·CHMe·OH	+0·7$_5$	55·8 [e, g]	75	+7
Pr·CMeEt·OH	+0·2$_5$	—[f]	—	≯±5
Ph·CMeEt·OH Ph·CMeEt·O·CO·R′	+0·3$_5$	18·1 [f, g]	50	+3 [h] +10 [h]
α-Tet. OH α-Tet. O·CO·R′	—	32·7 [i]	20 [j]	− ≯±5 [j] ≯±1 [j]

Notes: R′ = *o*-C_6H_4·CO_2H. α-Tet. = 1 : 2 : 3 : 4-tetrahydro-1-naphthyl. Specific rotations (in chloroform unless otherwise stated) are marked °.

[a] Davies and Feld, *J.*, 1956, 665. [b] Downer and Kenyon, *J.*, 1939, 1156. [c] Pickard and Kenyon, *J.*, 1911, **99**, 45; Kenyon and Wotton, unpublished work. [d] Kenyon and Partridge, *J.*, 1936, 128; this paper, Experimental. [e] Collyer and Kenyon, *J.*, 1940, 676. [f] Davies, Kenyon, and Salamé, *J.*, 1957, 3148. [g] Zeiss, *J. Amer. Chem. Soc.*, 1951, **73**, 2391. [h] Davies, *J.*, 1958, 3474. [i] Davies and White, *J.*, 1952, 3300. [j] In benzene solution. By direct resolution; Ikeda, *Bull. Lib. Arts Coll. Wakayama Univ.*, 1954, **4**, 27.

1 : 2 : 3 : 4-Tetrahydro-1-naphthol and its hydrogen phthalate give the inactive hydroperoxide, and 1-phenylethanol and 1-phenylpropanol react with racemisation accompanied by inversion of configuration. These reactions probably proceed by an S_Ni mechanism as we have described earlier.[2,4,5] The reaction of ethyl 1-phenylethyl ether must proceed

[3] Williams and Mosher, *J. Amer. Chem. Soc.*, 1954, **76**, 3495.
[4] (*a*) Davies, Foster, and White, *J.*, 1953, 1541; (*b*) *idem*, *J.*, 1954, 2200.
[5] Bassey, Bunton, Davies, Lewis, and Llewellyn, *J.*, 1955, 2471.

similarly (eqn. 1), although the reaction of phenyl 1-phenylethyl ether with hydrogen chloride has been shown to follow an S_Ni mechanism.[6]

$$Ph{\cdot}CHMe{\cdot}OEt \xrightarrow{H^+} EtOH + Ph{\cdot}\overset{+}{C}HMe \xrightarrow{HO{\cdot}OH} Ph{\cdot}CHMe{\cdot}O{\cdot}OH + H^+ \quad . \; . \; . \; . \; (1)$$

1-Phenylbutanol, 1-2′-naphthylethanol, and 2-phenylbutan-2-ol and its hydrogen phthalate, however, give the corresponding hydroperoxides with predominating retention of configuration. Our experiments with ^{18}O-labelled reactants,[1,5] supported by the general absence of reactions leading to the heterolytic formation of the O–O bond,[7] render it unlikely that these reactions follow a process other than one involving alkyl–oxygen fission. They therefore appear to proceed by an S_Ni mechanism,[1] *e.g.*, eqn. (2).

$$+ \quad H^+ \quad + \quad H_2O \quad . \; . \quad (2)$$

Experimental

In experiments involving concentrated hydrogen peroxide, precautions were taken against explosion.

1-Phenylethyl Compounds.—The preparation and reduction of the active hydroperoxide and its triphenylmethyl and 9-xanthenyl derivatives, obtained from the active alcohol, are described in Part IV.[2]

Hydroperoxide from the ethyl ether. (−)-Ethyl 1-phenylethyl ether (0·75 g.), α_D^{18} −73·52° (*l* 1; undild.), was caused to react with hydrogen peroxide (8 c.c.) containing concentrated sulphuric acid (0·1 g.).[8] Impure 1-phenylethyl hydroperoxide (0·30 g.), b. p. 55—60°/0·01 mm., α_D^{18} −1·48° (*l* 0·25; undiluted), was isolated, but retained the characteristic odour of the ether. A fraction (0·2 g.) was therefore converted into the triphenylmethyl derivative (0·49 g.) which (uncrystallised) had m. p. 70—74°, mixed m. p. 73—77°, $[\alpha]_D^{18}$ +7·28° (*l* 0·5; *c* 4·9 in $CHCl_3$), and after recrystallisation from ethanol, m. p. and mixed m. p. 80—81°.

In a second experiment the (+)-ether, α_D^{16} +12·12° (*l* 0·5; undiluted), after 12 hr. similarly gave a mixture of the hydroperoxide and unchanged ether, α_D^{22} +2·29° (*l* 0·5; undiluted), b. p. 50—56°/0·001 mm., which could not be separated by distillation. From this, the triphenylmethyl derivative was obtained in 70% yield, $[\alpha]_D^{17}$ −1·87° (*l* 2; *c* 4·8 in $CHCl_3$), m. p. 79—81°, mixed m. p. with a pure sample with $[\alpha]_D^{18}$ −1·35° (*l* 2; *c* 4·8 in $CHCl_3$), 78—80°.

These two experiments give values of $[\alpha]_{IIa}/[\alpha]_{Ia}$ of −0·099 and −0·154 respectively (mean −0·13); $\alpha_{Ia}/\alpha_I \geqslant +1{\cdot}68$;[9] $\alpha_{III}/\alpha_{II} = +0{\cdot}31$;[2] and $\alpha_{II}/[\alpha]_{IIa} = +1{\cdot}54$.[2]

Reduction of the hydroperoxide with triphenylphosphine. Triphenylphosphine (2·21 g.) in pentane was added dropwise to 1-phenylethyl hydroperoxide (1·16 g.), α_D^{25} −1·94° (*l* 1; undiluted), suspended in pentane; the solvent boiled under reflux, and triphenylphosphine oxide (m. p. 150°) separated.[10] The filtrate was washed with dilute aqueous hydrogen peroxide, and with water, and dried (K_2CO_3). Distillation gave 1-phenylethanol, b. p. 104°/16 mm., $n_D^{25\cdot8}$ 1·5256, α_D^{19} −0·60 (*l* 1; undiluted), whence $\alpha_{III}/\alpha_{II} = +0{\cdot}31$.

The reduction of the hydroperoxide with phenylboronic acid had a value $\alpha_{III}/\alpha_{II} = +0{\cdot}34$.[11] These two values correlate well with the mean value of +0·31 which we have obtained previously with different reducing agents.[2]

1-Phenylpropyl Compounds.—Hydroperoxide from the alcohol. (±)-1-Phenylpropanol (3·0 g.) was added dropwise and with stirring to a mixture of 90% hydrogen peroxide (10 c.c.) and concentrated sulphuric acid (0·1 g.) at 0°. After 1 hr. the mixture was allowed to warm to room temperature and stirring was continued for a further 5 hr. Water (50 c.c.) was added and the organic layer extracted with ether, and the extract washed with saturated aqueous sodium

[6] Hart and Eleuterio, *J. Amer. Chem. Soc.*, 1954, **76**, 1379.
[7] Bassey and Davies, unpublished work; M. Bassey, Thesis, London, 1958.
[8] Davies and Feld, *J.*, 1956, 4669.
[9] Phillips and Kenyon, *J.*, 1930, 1694; Hughes, Ingold, and Scott, *J.*, 1937, 1201.
[10] Cf. Horner and Jurgeleit, *Annalen*, 1955, **591**, 138.
[11] Davies and Moodie, *J.*, 1958, 2372.

XUM

hydrogen carbonate, and dried (Na_2SO_4). Distillation yielded 1-*phenylpropyl hydroperoxide* (2·43 g.), b. p. 52—54°/0·001 mm., n_D^{20} 1·5190 (Found: C, 71·2; H, 8·1. $C_9H_{12}O_2$ requires C, 71·0; H, 8·0%).

The (+)-alcohol (2·1 g.), α_D^{21} +10·84° (*l* 1; undiluted), similarly gave the (−)-hydroperoxide (1·89 g.), b. p. 64°/0·07 mm., n_D^{20} 1·5192, α_D^{21} −0·93° (*l* 1; undiluted), whence $\alpha_{II}/\alpha_I = -0{\cdot}086$.

From the (−)-alcohol (0·9 g.), α_D^{20} −12·15° (*l* 0·5; undiluted), the (+)-hydroperoxide (0·67 g.) was obtained, b. p. 54—56°/0·005 mm., α_D^{18} +1·51° (*l* 0·5; undiluted), whence $\alpha_{II}/\alpha_I = -0{\cdot}124$, giving a mean value of −0·10.

1-*Phenylpropyl triphenylmethyl peroxide.* The (±)-hydroperoxide (1·0 g.) in acetic acid (5 c.c.) was added to a solution of triphenylmethanol (1·98 g.) and concentrated sulphuric acid (1 drop) in acetic acid (10 c.c.). After 2 hr. the mixture was poured on crushed ice (50 c.c.) yielding a solid (2·03 g.) which was recrystallised four times from aqueous ethanol giving 1-*phenylpropyl triphenylmethyl peroxide*, m. p. 78° (Found: C, 85·2; H, 6·3. $C_{28}H_{26}O_2$ requires C, 85·2; H, 6·6%).

Similarly the (+)-hydroperoxide (0·34 g.), α_D^{18} +1·51° (*l* 0·5; undiluted), and triphenylmethanol (0·59 g.) gave the dialkyl peroxide (0·76 g.), m. p. 84—86°, $[\alpha]_D^{13}$ +2·01° (*l* 0·5; *c* 5·0 in $CHCl_3$).

1-*Phenylpropyl 9-xanthenyl peroxide.* (±)-1-Phenylpropyl hydroperoxide (0·20 g.) in acetic acid (3 c.c.) was added to xanthhydrol (0·26 g.) in acetic acid (5 c.c.). After 2 hr. the mixture was poured into water giving an oil which later solidified (0·29 g.). Four recrystallisations from ethanol gave 1-*phenylpropyl 9-xanthenyl peroxide*, m. p. 69—70° (Found: C, 79·1; H, 6·1. $C_{22}H_{20}O_3$ requires C, 79·5; H, 6·1%).

Reduction of the hydroperoxide with sodium sulphite. The hydroperoxide (1·50 g.), α_D^{21} −0·93° (*l* 1; undiluted), was shaken for 6 hr. with aqueous sodium sulphite (6·25 g. of the heptahydrate in 50 c.c. of water). An ethereal extract gave 1-phenylpropanol, b. p. 109—110°/15 mm., with a negative peroxide test, α_D^{19} −0·22° (*l* 1; undiluted), n_D^{20} 1·5224, whence $\alpha_{III}/\alpha_{II} = +0{\cdot}24$.

1-*Phenylbutyl Compounds.*—The optically pure alcohol, m. p. 49°, $[\alpha]_D^{18}$ −45·9° (in C_6H_6),[12] has $[\alpha]_D^{18}$ −51·4° (*l* 2; *c* 5·0 in $CHCl_3$). Optically impure alcohol may be liquid; the rotatory power of the undiluted alcohol is then related to that of its chloroform solution by the factor $[\alpha]_D$ (in $CHCl_3$)/α_D (*l* 1; undiluted) = +1·66.

Hydroperoxide from the alcohol. A mixture of 1-phenylbutanol (1·0 g.) and 90% hydrogen peroxide (5 c.c.) containing sulphuric acid (0·1 g.) was vigorously stirred for 10 hr., yielding 1-phenylbutyl hydroperoxide (0·52 g.), b. p. 62°/0·001 mm., n_D^{20} 1·5128, d_4^{20} 1·023. Ivanov, Savinova, and Zhakovskaya [13] prepared the same compound by autoxidation of butylbenzene and report b. p. 56°/0·006 mm., n_D^{20} 1·5103, d_4^{20} 1·016.

(+)-1-Phenylbutanol (6·0 g.), $[\alpha]_D^{20}$ +42·41° (*l* 1; *c* 10 in $CHCl_3$) was treated similarly, a little ether being added to increase the mutual solubility of the two phases. The (+)-hydroperoxide (4·4 g.) was isolated, b. p. 66°/0·1 mm., α_D^{21} +4·21° (*l* 1; undiluted) n_D^{20} 1·5120, d^{20} 1·020 (Found: C, 72·6; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·5%). A second preparation from the same alcohol gave the hydroperoxide, b. p. 66°/0·01 mm., α_D^{21} +2·04° (*l* 1; undiluted), n_D^{20} 1·5122. In the absence of sulphuric acid, no reaction occurred.

Likewise the (−)-alcohol (4·0 g.), $[\alpha]_D^{18}$ −51·4° (*l* 2; *c* 5·0 in $CHCl_3$), gave the (−)-hydroperoxide (3·80 g.), b. p. 58°/0·005 mm., n_D^{20} 1·5123, α_D^{18} −2·14° (*l* 0·5; undiluted). A second preparation from the same alcohol (1·75 g.) gave the hydroperoxide (1·20 g.), α_D^{17} −1·71° (*l* 0·5; undiluted). A third specimen of the alcohol (2·4 g.), $[\alpha]_D^{18}$ −50·0° (*l* 2; *c* 5·6 in $CHCl_3$) gave the hydroperoxide (1·97 g.), b. p. 59—61°/0·005 mm., n_D^{20} 1·5120, α_D^{20} −2·96° (*l* 1; undiluted).

These five experiments give values of $\alpha_{II}/[\alpha]_I$ of +0·099, +0·048, +0·083, +0·067, and +0·118 respectively (mean of +0·083).

1-*Phenylbutyl triphenylmethyl peroxide.* By the usual method, the hydroperoxide (0·20 g.) and triphenylmethanol (0·33 g.) gave 1-*phenylbutyl triphenylmethyl peroxide* (0·48 g., from aqueous ethanol), m. p. 55·5—57° (Found: C, 85·1; H, 7·1. $C_{29}H_{28}O_2$ requires C, 85·2; H, 6·9%).

The (−)-hydroperoxide (2·0 g.), α_D^{20} −2·96° (*l* 1; undiluted), similarly gave the (−)-dialkyl peroxide (4·2 g.), m. p. 55·5—57·5°, $[\alpha]_D^{17}$ −2·18° (*l* 2; *c* 5·03 in $CHCl_3$); the (−)-hydroperoxide, α_D^{17} −2·14° (*l* 0·5; undiluted), gave the crude dialkyl peroxide having $[\alpha]_D^{18}$ −3·08° (*l* 1; *c* 5·2 in $CHCl_3$), and after one recrystallisation, $[\alpha]_D^{18}$ −2·56° (*l* 1; *c* 4·7 in $CHCl_3$).

The differing values of $\alpha_{II}/[\alpha]_{IIa}$ for these two experiments indicate that fractionation of the

[12] Kenyon and Partridge, *J.*, 1936, 128.
[13] Ivanov, Savinova, and Zhakovskaya, *Zhur. obshchei Khim.*, 1952, **22**, 781.

(−)- and (±)-dialkyl peroxide accompanies its isolation. In the reduction of this derivative (below), therefore, only the sign and not the magnitude of $\alpha_{III}/[\alpha]_{IIa}$ is significant.

1-Phenylbutyl 9-xanthenyl peroxide. A solution of the (±)-hydroperoxide (0·20 g.) and xanthhydrol (0·24 g.) in acetic acid (5 c.c.) yielded *1-phenylbutyl 9-xanthenyl peroxide* (0·34 g., from aqueous ethanol), m. p. 68·5° (Found: C, 79·2; H, 6·3. $C_{23}H_{22}O_3$ requires C, 79·7; H, 6·4%).

The (+)-hydroperoxide (0·50 g.), α_D^{21} +2·04° (*l* 1; undiluted), gave the (+)-dialkyl peroxide (0·94 g.), m. p. 59—63°, $[\alpha]_D^{22}$ +3·13° (*l* 0·5; *c* 6·2 in C_6H_6). Crystllisation from aqueous ethanol gave two fractions: (i) less soluble, m. p. 65°, $[\alpha]_D^{19}$ +2·32° (*l* 0·5; *c* 5·4 in C_6H_6), and (ii) more soluble, m. p. 61—65°, $[\alpha]_D^{18}$ +4·5° (*l* 0·5; *c* 4·9 in C_6H_6).

Reduction of the hydroperoxide. (i) *With sodium sulphite.* The (±)-hydroperoxide (1·0 g.) was shaken with aqueous sodium sulphite (4·5 g. of the heptahydrate in 36 c.c. of water) for 6 hr., yielding 1-phenylbutanol, b. p. 121°/21 mm., hydrogen phthalate, m. p. 89—91°.

The (−)-hydroperoxide (0·90 g.), α_D^{17} −1·71° (*l* 0·5; undild.), was treated similarly, but the mixture was shaken for 12 hr. to ensure complete reaction. The (−)-alcohol was isolated (0·46 g.), b. p. 122°/20 mm., n_D^{20} 1·5178, α_D^{18} −0·58° (*l* 0·5; undiluted), equivalent to $[\alpha]_D^{18}$ −1·92° (in $CHCl_3$).

(ii) *With zinc and acetic acid.* Water (1 c.c.) and zinc (1·0 g.) were added to a solution of the (−)-hydroperoxide (1·0 g.), α_D^{17} −2·14° (*l* 0·5; undiluted), in acetic acid (5 c.c.). The mixture was warmed to 50°, whereupon the temperature rose spontaneously to 75°. After cooling, the filtrate from the mixture was made just acidic by the successive addition of sodium hydroxide and hydrochloric acid. An ethereal extract gave the (−)-alcohol (0·76 g.), α_D^{20} −0·68° (*l* 0·5; undiluted), equivalent to $[\alpha]_D$ −2·26° (in $CHCl_3$), b. p. 118°/20 mm., n_D^{20} 1·5176.

The above two experiments gave values of $[\alpha]_{III}/\alpha_{II}$ of +0·56 and +0·53 respectively (mean +0·55).

(iii) *With lithium aluminium hydride.* The (±)-hydroperoxide (0·40 g.) was reduced with lithium aluminium hydride (0·11 g.) as for 1-phenylethyl hydroperoxide,[3] yielding an oil (0·20 g.). Treatment of this with phthalic anhydride (0·2 g.) and pyridine (1·2 g.) for 5 hr. at 60° gave 1-phenylbutyl hydrogen phthalate (from carbon disulphide–light petroleum), m. p. and mixed m. p. 91°.

Reduction of 1-phenylbutyl triphenylmethyl peroxide with zinc and acetic acid. The (−)-peroxide (4·0 g.), $[\alpha]_D^{17}$ −2·18° (*l* 1; *c* 5·03 in $CHCl_3$), dissolved on warming in a mixture of acetic acid (40 c.c.) and water (5 c.c.). Zinc dust (5·0 g.) was added and the mixture kept at 80° for 30 min. (−)-1-Phenylbutanol (1·02 g.), b. p. 110°/15 mm., α_D^{17} −0·82° (*l* 1; undiluted), and triphenylmethanol (2·43 g.), m. p. 158—160°, were isolated.

A similar reduction of the specimen of the dialkyl peroxide (2·9 g.), $[\alpha]_D^{18}$ −2·56° (*l* 1; *c* 4·7 in $CHCl_3$) (see above), gave (−)-1-phenylbutanol (0·48 g.), b. p. 112°/16 mm., α_D^{20} −0·98° (*l* 1; undiluted), n_D^{20} 1·5181.

$[\alpha]_{III}/\alpha_{II}$ Derived from $[\alpha]_{III}/[\alpha]_{IIa} \times [\alpha]_{IIa}/\alpha_{II}$ is therefore positive, *i.e.*, the same stereochemical effect predominates in the sequence (II) ⟶ (IIa) ⟶ (III) as in the direct reduction (II) ⟶ (III).

1-2′-Naphthylethyl Compounds.—The hydroperoxide. (i) *From the alcohol.* (−)-1-2′-Naphthylethanol (3·0 g.), $[\alpha]_D^{17}$ −48·9° (*l* 1; *c* 4·8 in $CHCl_3$), was added with stirring to 90% hydrogen peroxide (10 c.c.) containing sulphuric acid (0·1 g.) at 0°. After 4 hours' stirring at room temperature a yellow oil (2·76 g.) was isolated which solidified after 1 week at 0°. Recrystallisation from a large volume of light petroleum gave (−)-*1-2′-naphthylethyl hydroperoxide*, m. p. 37—38°, $[\alpha]_D^{18}$ −3·34° (*l* 1; *c* 4·8 in $CHCl_3$) (Found: C, 76·8; H, 6·5. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%).

A second preparation gave the (−)-hydroperoxide [0·60 g. from 1·0 g. of the same (−)-alcohol], m. p. 36—38°, $[\alpha]_D^{19}$ −5·94° (*l* 1; *c* 5·2 in $CHCl_3$).

The above two experiments give values of $[\alpha]_{II}/[\alpha]_I$ of +0·068 and +0·121 respectively (mean +0·095).

(ii) *From the hydrogen phthalate.* The hydrogen phthalate (0·75 g.) was dissolved in 90% hydrogen peroxide (5 c.c.) containing sodium hydrogen carbonate (0·70 g.). After 12 hr. at 0° and 84 hr. at room temperature the initially clear solution was turbid. An ethereal extract of the diluted reaction mixture gave a solid (0·1 g.), m. p. 34—37°, mixed m. p. with the hydroperoxide from (i), 35—37°. Some hydrogen phthalate (0·52 g.), m. p. 90—91°, was recovered when the aqueous layer was acidified.

1-2′-*Naphthylethyl* 9-*xanthenyl peroxide*. By the usual method the (−)-hydroperoxide (60 mg.) gave **1-2′-*naphthylethyl* 9-*xanthenyl peroxide*** (from ethanol, 90 mg.), m. p. 100° (Found: C, 81·1; H, 5·3. $C_{25}H_{20}O_3$ requires C, 81·5; H, 5·5%). The optical rotation was not measured.

An attempt to prepare the triphenylmethyl derivative gave an oil which could not be caused to solidify.

Reduction of the hydroperoxide with zinc and acetic acid. Zinc (1·0 g.) was added to a solution of the (−)-hydroperoxide (0·60 g.), $[\alpha]_D^{19}$ −5·94° (*l* 1; *c* 5·2 in $CHCl_3$), in 85% acetic acid (25 c.c.). The mixture was warmed to 60° and then allowed to cool. After 2 hr. the mixture was filtered into water and steam-distilled, giving 1-2′-naphthylethanol (0·23 g.), m. p. 65—67°, $[\alpha]_D^{19}$ −4·42° (*l* 1; *c* 4·5 in $CHCl_3$), whence $[\alpha]_{III}/[\alpha]_{II} = +0·75$.

4-*Chlorodiphenylmethyl Compounds*.—*Hydroperoxide from the alcohol.* 4-Chlorodiphenylmethanol (0·5 g.) was added to 90% hydrogen peroxide (5 c.c.) containing concentrated sulphuric acid (0·1 g.) at 0°. The mixture was stirred at room temperature for 6 hr. and the crude hydroperoxide isolated as an oil (0·34 g.) which gave a strong peroxide test and could not be caused to solidify or distilled below 100°/0·001 mm.

A second preparation from the (+)-alcohol (2·0 g.), $[\alpha]_D^{18}$ +9·10° (*l* 1; *c* 5·0 in $CHCl_3$), similarly gave an intractable oil; its rotatory power was not measured.

Attempts were also made to prepare the hydroperoxide by solvolysis of the hydrogen phthalate in 90% hydrogen peroxide containing sodium hydrogen carbonate. Such solutions, however, are unstable and inflame about 3 hr. after preparation. If the solutions were diluted with water when this violent stage appeared imminent, the hydrogen phthalate could be recovered in 80% yield.

4-Chlorodiphenylmethyl triphenylmethyl peroxide. By the usual method the crude active hydroperoxide (0·50 g.) and triphenylmethanol (0·55 g.) gave a solid (0·81 g.), $[\alpha]_D^{21}$ −4·8° (*l* 2; *c* 2·8 in $CHCl_3$), m. p. 122—124°, which was recrystallised from ethanol giving ***4-chlorodiphenylmethyl triphenylmethyl peroxide***, m. p. 129° (Found: C, 80·5; H, 4·9; Cl, 6·7. $C_{32}H_{25}O_2Cl$ requires C, 80·6; H, 5·3; Cl, 7·4%).

A second sample of the crude hydroperoxide (0·70 g.) prepared from the same active alcohol (1·0 g.) gave the triphenylmethyl derivative (1·26 g.), m. p. 121—124°, $[\alpha]_D^{18}$ −0·4° (*l* 1; *c* 4·9 in $CHCl_3$).

1-*Ethyl*-1-*methylbutyl Compounds*.—*Hydroperoxide from the alcohol.* The alcohol (0·73 g.), α_D^{16} −0·36° (*l* 1; undiluted[14]), n_D^{20} 1·4225, gave 1-ethyl-1-methylbutyl hydroperoxide[4b] (0·54 g.), b. p. 40—41°/0·5 mm., n_D^{25} 1·4267, α_D^{19} +0·08° (*l* 1; undiluted).

In a second experiment the alcohol (0·54 g.), n_D^{20} 1·4224, b. p. 58—59°/25 mm., α_D^{19} +0·20° (*l* 1; undild.), yielded the hydroperoxide (0·34 g.), b. p. 38°/0·1 mm., n_D^{25} 1·4269, α_D^{19} 0·00° (*l* 0·5; undiluted), and the hydrogen perphthalate,[4b] m. p. 90°, mixed m. p. 90—92°, $[\alpha]_D^{19}$ 0·00° (*l* 1; *c* 10 in EtOH and in $CHCl_3$).

Reduction of the hydroperoxide with sodium sulphite. The (+)-hydroperoxide (0·54 g.), α_D^{19} +0·08°, was reduced by shaking it for 17 hr. with a solution of sodium sulphite (3·8 g.) in water (7 c.c.). The alcohol was recovered, b. p. 62°/*ca.* 25 mm., n_D^{25} 1·4197, $[\alpha]_D^{19}$ 0·0° (*l* 0·5; *c* 50 in EtOH).

1-*Methyl*-1-1′-*naphthylpropyl Compounds*.—*Hydroperoxide from the alcohol.* The alcohol[15] (1·0 g.) in ether (1 c.c.) was added dropwise with stirring at 0° to 90% hydrogen peroxide (7 c.c.) containing concentrated sulphuric acid (0·05 c.c.). The mixture was allowed to warm to room temperature, and stirring was continued for a further 3 hr. The hydroperoxide was isolated as a yellow oil, b. p. >100°/0·001 mm., which could not be caused to solidify.

Hydroperoxide from the hydrogen phthalate. A solution of the hydrogen phthalate (0·75 g.) in 90% hydrogen peroxide (7 c.c.) containing sodium hydrogen carbonate (0·8 g.) was kept at 0° for 96 hr. Dilution with water (50 c.c.) gave the hydroperoxide (0·33 g.) as a yellow oil. On acidification of the aqueous layer, some of the hydrogen phthalate (0·17 g.) was recovered.

In a similar experiment the (+)-hydrogen phthalate (0·92 g.), $[\alpha]_D$ +51·6° (*l* 2; *c* 4·0 in EtOH), yielded the hydroperoxide, $[\alpha]_D^{16}$ −6·33° (*l* 0·5; *c* 5·9 in $CHCl_3$).

Solutions of the sodium alkyl phthalate in hydrogen peroxide are unstable at room temperature and inflame after about 3 hr.

1-*Methyl*-1-1′-*naphthylpropyl triphenylmethyl peroxide*. The crude (±)-hydroperoxide (0·21

[14] Davies, Kenyon, and Salamé, *J.*, 1957, 3148.
[15] Davies, Kenyon, and Thaker, *J.*, 1957, 3151.

g.) gave the (±)-*triphenylmethyl derivative* (0·44 g., from aqueous methanol), m. p. 114° (Found: C, 86·4; H, 6·6. $C_{33}H_{30}O_3$ requires C, 86·4; H, 6·6%).

Similarly the (−)-hydroperoxide (0·29 g.), $[\alpha]_D^{16}$ −6·33° (*l* 0·5; *c* 5·9 in $CHCl_3$), gave the (−)-triphenylmethyl derivative (0·35 g.), m. p. 107—112°, $[\alpha]_D^{17}$ −6·28° (*l* 0·5; *c* 3·5 in $CHCl_3$) before crystallisation.

We thank Professors E. D. Hughes, F.R.S., and Sir Christopher Ingold, F.R.S., and Dr. J. Kenyon, F.R.S., for their interest and encouragement, and Dr. Kenyon for the gift of some of the optically active compounds. This work was carried out during the tenure of an Edwin Tate and Holl Scholarship (by R. F.).

Chemistry Department, Battersea College of Technology, London, S.W.11.
William Ramsay and Ralph Forster Laboratories, University College, London, W.C.1.

[*Received, August 8th*, 1958.]

---

935. *The Conductances of Some Chlorides in Ethanol. Part II.*[1] *Electrolytic Behaviour of Zirconium Chloride Ethoxides.*

By A. M. El-Aggan, D. C. Bradley, and W. Wardlaw.

The conductances of zirconium chloride ethoxides, $ZrCl_n(OEt)_{4-n}$, where $n = 3$, 2, or 1, have been measured in very dilute solution in ethanol at 25° over a range of concentrations. The limiting molar conductances and the variation of conductance with concentration suggest in each case the presence of solvolytic equilibria involving the formation of hydrochloric acid. However, it does not seem possible to determine the precise nature of these equilibria from conductance data alone.

Recently [1] we studied the electrolytic behaviour of alcoholic solutions of hydrochloric acid, cæsium chloride, magnesium chloride, and lanthanum chloride in order to obtain information to interpret the electrolytic behaviour of Group IV metal chlorides. Now we report the conductances of three zirconium chloride ethoxides. Zirconium tetrachloride reacts with ethyl alcohol [2] and was not included in this study.

The aqueous solution chemistry of zirconium is complicated by hydrolysis and hydrolytic polymerisation and it seemed reasonable to expect a much simpler situation in solutions of chloride ethoxides in ethyl alcohol. Moreover, the results were expected to throw some light on the problem of the mechanism of formation of zirconium tetra-alkoxides.

Experimental

*Zirconium Monochloride Triiso*propoxide.—Zirconium *iso*propoxide solvate (18·7 g.) in benzene (100 c.c.) was treated with acetyl chloride (3·8 g.). After boiling for 2 hr. the solution was evaporated to dryness under reduced pressure and the monochloride tri*iso*propoxide *solvate* (10 g.) obtained after two recrystallisations from benzene [Found: Zr, 25·4; Cl, 9·8; Pr^iO, 64·7. $ZrCl(OPr^i)_3.Pr^iOH$ requires Zr, 25·1; Cl, 9·7; Pr^iO, 64·9%].

*Zirconium Dichloride Diiso*propoxide.—Zirconium *iso*propoxide solvate (7·2 g.) was caused to react with acetyl chloride (2·9 g.) in benzene (100 c.c.), and the solid product isolated as before. The dichloride di*iso*propoxide *solvate* was purified by three recrystallisations from carbon tetrachloride [Found: Zr, 26·9; Cl, 20·7; Pr^iO, 52·1. $ZrCl_2(OPr^i)_2.Pr^iOH$ requires Zr, 26·8; Cl, 20·8; Pr^iO, 52·1%].

Zirconium Trichloride Monoethoxide.—Zirconium tetrachloride (17·9 g.) suspended in benzene (250 c.c.) was treated with a mixture of ethyl alcohol (7·05 g.) and benzene (100 c.c.). After boiling for 1½ hr. the solution was filtered and the filtrate evaporated to dryness under reduced pressure. The pure trichloride monoethoxide *solvate* was obtained after four

[1] Part I, Aggan, Bradley, and Wardlaw, *J.*, 1958, 2092.
[2] Bradley, Halim, and Wardlaw, *J.*, 1950, 3450.

XUM

recrystallisations from benzene [Found: Zr, 31·7; Cl, 36·7; EtO, 31·1. $ZrCl_3(OEt)$,EtOH requires Zr, 31·6; Cl, 36·8; EtO, 31·2%].

Measurement of Conductances in Ethyl Alcohol.—The methods of preparation of " conductivity " alcohol, of solutions of the zirconium chloride alkoxides in the alcohol, and the apparatus used for the measurement of conductances have been described.[1] All measurements were at 25°.

Results and Discussion

Zirconium Monochloride Triisopropoxide.—The conductances were measured at several concentrations in the range 10^{-5}—$1{\cdot}5 \times 10^{-4}$M and did not change with time. Although the monochloride tri*iso*propoxide was used because it can be purified more readily than the monochloride triethoxide, alcohol interchange ensures that it is the behaviour of the monochloride triethoxide which is studied. The results are given in Table 1 where Λ_m is the molar conductance and C_m the concentration in moles/litre. A plot of $\Lambda_m C_m$ against $1/\Lambda_m$ showed that the simple Ostwald equation was obeyed and $\Lambda_{calc.}$ (in Table 1) is the value calculated from this with the apparent limiting conductance $\Lambda_0' = 72{\cdot}31$ and $K' = 1{\cdot}087 \times 10^{-4}$.

Table 1.

$10^5 C_m$	Λ_m	$\Lambda_{calc.}$	$10^5 K$	$10^5 C_m$	Λ_m	$\Lambda_{calc.}$	$10^5 K$
1·165	65·99	65·88	9·42	6·165	51·47	51·50	9·86
2·067	62·18	62·11	9·75	7·029	49·92	49·97	9·82
2·530	60·63	60·50	9·87	8·262	47·86	48·03	9·69
3·062	58·72	58·83	9·70	9·651	46·16	46·15	9·84
3·630	57·13	57·20	9·78	11·314	44·12	44·19	9·75
4·345	55·34	55·38	9·85	13·227	42·23	42·26	9·76
5·261	53·28	53·27	9·85	15·280	40·51	40·47	9·78

The excellent agreement between Λ_m and $\Lambda_{calc.}$ is reflected in the percentage standard deviation of $\pm 0{\cdot}15\%$. To allow for interionic effects the results were treated by Fuoss's method[2] with use of the simple expression for the mean activity coefficient: $-\log f_\pm^2 = 5{\cdot}954\sqrt{(\alpha C_m)}$, where α is the degree of ionisation. This gave the limiting equivalent conductance $\Lambda_0 = 73{\cdot}65$ and the thermodynamic dissociation constant $K = 9{\cdot}78 \times 10^{-5}$. Values for K given in Table 1 were computed for each experimental point. This procedure is very sensitive to experimental error but the percentage standard deviation of $\pm 0{\cdot}9\%$ for K and the distribution of sign in the deviations leaves no doubt that the zirconium monochloride triethoxide behaves as a weak uni-univalent electroyte in ethyl alcohol. Zirconium tetra*iso*propoxide behaves as a non-electrolyte in ethyl alcohol, so part of the conductance of zirconium monochloride triethoxide must be attributed to ionisation of the chlorine. However, the limiting conductance is very high for a univalent chloride, being near to that (82·46 [1]) for hydrochloric acid. Therefore, a simple ionisation of the type

$$ZrCl(OEt)_3 \rightleftharpoons Zr(OEt)_3^+ + Cl^- \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

seems improbable because this would require a Λ_0 of *ca.* 50 (cf. CsCl 48·01 [1]). Solvolysis seems indicated, *i.e.*,

$$ZrCl(OEt)_3 + EtOH \rightleftharpoons Zr(OEt)_4 + H^+ + Cl^- \quad . \quad . \quad . \quad . \quad (2)$$

This would require a linear relation between $(\Lambda_m C_m)^2$ and $1/\Lambda_m$, which is not found. The simultaneous operation of mechanisms (1) and (2) would cause $\Lambda_m C_m$ to be independent of C_m which is also contrary to our results. A fourth possibility is complete ionisation in (1) with simultaneous reversible solvation as in (3):

$$Zr(OEt)_3^+ + EtOH \rightleftharpoons Zr(OEt)_4 + H^+ \quad . \quad . \quad . \quad . \quad . \quad (3)$$

[2] Fuoss, *J. Amer. Chem. Soc.*, 1935, **57**, 488.

This would require the following relation between Λ_m and C_m:

$$\{K_3[\lambda^\circ_{H^+} - \lambda^\circ_{Zr(OEt)_3^+}](\Lambda^\circ_{HCl} - \Lambda_m)\}^{\frac{1}{2}}/C_m^{\frac{1}{2}} = \Lambda_m - [\lambda^\circ_{Zr(OEt)_3^+} + \lambda^\circ_{Cl^-}] \quad . \quad (4)$$

Thus a plot of $(\Lambda^\circ_{HCl} - \Lambda_m)^{\frac{1}{2}}/C_m^{\frac{1}{2}}$ against Λ_m should be linear but this was not the case when $\Lambda^\circ_{HCl} = 82{\cdot}46$ was used. A straight line resulted from $\Lambda^\circ_{HCl} = 73{\cdot}65$ but the values of the term in the last bracket of eqn. (4) then obtained by substitution in eqn. (4) were impossibly low. Finally, in view of the proximity of Λ_0 to the value for hydrochloric acid we considered the possibility of complete solvolysis, *i.e.*,

$$ZrCl(OEt)_3 + EtOH \longrightarrow Zr(OEt)_4 + H^+ + Cl^- \quad . \quad . \quad . \quad . \quad (5)$$

The solution of zirconium monochloride triethoxide would then behave electrolytically like hydrochloric acid of the same molar concentration. Unfortunately this also is not the case because we have previously shown [1] for hydrochloric acid that $K = 8{\cdot}23 \times 10^{-3}$ whereas the data in Table 1 show clearly that $K = 9{\cdot}78 \times 10^{-5}$. The only remaining possibility is that the monochloride ionises according to equation (1) but that the solvated ion $Zr(OEt)_3^+$ has an anomalously high mobility due to some special mechanism of conduction.

Zirconium Dichloride Diisopropoxide.—The molar conductances for the dichloride over the concentration range 5—50 $\times 10^{-5}$ molar gave a convincing Ostwald plot as shown by the agreement between Λ_m and $\Lambda_{calc.}$ in Table 2. Values of $\Lambda_{calc.}$ were computed by use

TABLE 2.

10^5C_m	Λ_m	$\Lambda_{calc.}$	10^5K	10^5C_m	Λ_m	$\Lambda_{calc.}$	10^5K
4·756	97·07	97·11	9·79	11·79	75·12	74·90	10·16
5·609	92·56	93·20	9·65	14·18	70·51	70·51	10·09
6·584	89·28	89·28	9·97	16·88	66·24	66·39	10·02
7·737	85·76	85·25	10·19	22·02	60·35	60·33	10·06
8·899	81·82	81·80	10·04	50·45	43·58	43·66	9·81
10·10	79·09	78·69	10·21				

of the apparent limiting molar conductance $\Lambda_0' = 144{\cdot}1$ and $K' = 6{\cdot}644 \times 10^{-5}$ and the percentage standard deviation was $\pm 0{\cdot}37\%$.

The high value of Λ_0' [almost twice that for $ZrCl(OEt)_3$] again suggested the formation of hydrochloric acid and we explored the possibility of complete solvolysis:

$$ZrCl_2(OEt)_2 + 2EtOH \longrightarrow Zr(OEt)_4 + 2H^+ + 2Cl^- \quad . \quad . \quad . \quad . \quad (6)$$

Fuoss's method [3] was applied to the data in the form of *equivalent* conductances and normalities (based on eqn. 6). Activities were calculated as for the monochloride and the appropriate functions of Fuoss's treatment gave the required linear relationship. The limiting *equivalent* conductance was 77·15 and the thermodynamic dissociation constant $K = 9{\cdot}99 \times 10^{-5}$. The calculated values of K are also shown in Table 2. As in the case of the monochloride, other relationships between Λ_m and C_m corresponding to alternative mechanisms of ionisation were singularly unsuccessful in accounting for the results.

Zirconium Trichloride Monoethoxide.—The most striking feature of the results was the appearance of two intersecting straight lines in the plot of $\Lambda_m C_m$ against $1/\Lambda_m$, thus recalling the behaviour of lanthanum trichloride.[1] The results at the highest dilution ($C_m = 10^{-5}$—10^{-4}M) gave an apparent limiting molar conductance $\Lambda_0' = 252{\cdot}4$ and $K' = 7{\cdot}67 \times 10^{-5}$ and the data are shown in Table 3.

TABLE 3.

10^5C	Λ_m	$\Lambda_{calc.}$	10^4K	10^5C_m	Λ_m	$\Lambda_{calc.}$	10^4K
0·8347	227·7	229·4	1·76	4·8329	175·1	175·5	2·02
1·3252	219·6	219·6	2·02	5·6770	167·8	168·8	1·98
2·0342	208·7	207·4	2·13	6·5978	162·3	162·5	2·02
2·7400	198·4	197·2	2·12	7·5786	156·4	156·5	2·05
3·4458	188·4	188·9	1·93	8·8614	149·8	149·8	2·01
4·0766	183·5	182·5	2·10	10·336	144·1	143·1	2·04

Alternatively, the assumption of complete solvolysis:

$$ZrCl_3(OEt) + 3EtOH \longrightarrow Zr(OEt)_4 + 3H^+ + 3Cl^- \quad . \quad . \quad . \quad . \quad (7)$$

and application of Fuoss's treatment to *equivalent* conductances and normalities gave the limiting *equivalent* conductance $\Lambda_0 = 85{\cdot}85$ and the thermodynamic dissociation constant $K = 2{\cdot}02 \times 10^{-4}$. Calculated values for K are also given in Table 3. The results for the more concentrated solutions ($C_m = 1{\cdot}8$—$3{\cdot}9 \times 10^{-4}$M) are extremely interesting in resembling those for the *dichloride*. A plot of $\Lambda_m C_m$ against $1/\Lambda_m$ gave a straight line corresponding to an apparent limiting molar conductance $\Lambda_0' = 150{\cdot}1$ (cf. the dichloride 144·1) and $K' = 6{\cdot}96 \times 10^{-4}$. The deviations of Λ_m from $\Lambda_{calc.}$ showed a percentage standard deviation of $\pm 0{\cdot}15\%$. The data are given in Table 4.

Again the alternative treatment of using *equivalent* conductances (assuming equiv. =

TABLE 4.

C_m	1·8201	2·1292	2·7213	3·8731
Λ_m	123·8	120·5	115·1	107·4
$\Lambda_{calc.}$	123·5	120·5	115·3	107·3
10^3K	1·017	1·012	1·008	1·017

$\frac{1}{2}M$) and normalities and applying Fuoss's treatment gave a satisfactory interpretation of the results with the limiting *equivalent* conductance $\Lambda_0 = 79{\cdot}5$ and $K = 1{\cdot}013 \times 10^{-3}$. This behaviour of the trichloride is strongly indicative of successive ionisations and does not support the suggestion of complete solvolysis. The most striking feature of the results for these three compounds is the proximity of Λ_0 in each case to that for hydrochloric acid as shown in the summary of the data in Table 5.

TABLE 5.

Compound	Λ_0 *	10^5K	Λ_0' †	$10^5K'$
$ZrCl(OEt)_3$	73·65	9·78	—	—
$ZrCl_2(OEt)_2$	77·15	9·99	144·1	6·64
$ZrCl_3(OEt)$ (*a*)	85·85	20·2	252·4	7·67
,, (*b*)	79·5	101·3	150·1	69·6
HCl	82·46	823	—	—

* From equivalent conductances. † From molar conductances.
(*a*) Most dilute region; (*b*) lower dilution.

It is noteworthy that Λ_0 increases steadily from the monochloride to the trichloride whereas if the charged species $Zr(OEt)_3^+$, $Zr(OEt)_2^{2+}$, and $Zr(OEt)^{3+}$ were involved we should expect the opposite trend in Λ_0. Moreover, solvolysis becomes increasingly more probable in passing from the monochloride to the trichloride. It is clear that other experimental work involving a different technique will be required to resolve this complex situation but we are inclined to the view that solvolytic equilibria of the type depicted in eqn. (2) are involved.

One of us (A. M. A.) thanks the Egyptian Government for a Grant and Alexandria University for study-leave.

BIRKBECK COLLEGE, MALET STREET, LONDON, W.C.1. [*Received, August 6th*, 1958.]

936. *Some Chloride Alkoxides of Quadrivalent Vanadium and Quinquevalent Molybdenum.*

By D. C. Bradley, R. K. Multani, and W. Wardlaw.

Vanadium tetrachloride reacts with alcohols in cold benzene forming the dichloride dialkoxide alcoholates $VCl_2(OR)_2$,ROH (I), where R = Me, Et, Pr^n, Pr^i, Bu^n, Bu^i, Bu^s, and *n*-pentyl. Under more vigorous conditions, and especially with tertiary alcohols, hydrolytic side reactions occur. Heating the dichloride dialkoxide alcoholates at 150°/0·1 mm. formed vanadium oxychloride alkoxides, $V_2OCl_3(OR)_3$. The alcoholates (I; R = Me or Pr^i) were dimeric in boiling benzene, suggesting hexaco-ordinated vanadium. Molybdenum pentachloride reacts with alcohols forming the dimeric trichloride dialkoxides $MoCl_3(OR)_2$ (II), where R = Me, Et, or Pr^n, in which molybdenum is probably hexaco-ordinated. These compounds decomposed at temperatures above 80° *in vacuo* and gave molybdenum oxychloride alkoxides. Both di- and tri-chloride alkoxides (I) and (II) exchanged alkoxide groups with alcohols.

The tetrachlorides of titanium, zirconium, and thorium[1] show decreased reactivity towards alcohols with increase in atomic number of the metal. Little is known of the chemistry of vanadium tetrachloride because of its instability and it was of interest to study its reactivity with alcohols to compare it with the Group IVA tetrachloride.[3] Knowledge of the reactivity of vanadium tetrachloride was also required for the possible preparation of vanadium tetra-alkoxides. Similarly the reactivity of molybdenum pentachloride with alcohols was of interest for comparison with that of the pentachlorides of niobium and tantalum and in connection with the preparation of molybdenum pentaalkoxides.

Reactions of Vanadium Tetrachloride with Alcohols.—Vanadium tetrachloride reacted with several alcohols: $VCl_4 + 3ROH \longrightarrow VCl_2(OR)_2,ROH + 2HCl$; where R = Me, Et, Pr^n, Pr^i, Bu^n, Bu^i, Bu^s or *n*-pentyl. It thus resembles titanium tetrachloride in reactivity and it appears that a change of one unit in atomic number has had little effect. Although vanadium tetrachloride dissociates to the trichloride at an appreciable rate even at room temperature the dichloride dialkoxide alcoholates are stable dark-green solids which are dimeric in boiling benzene. The dimers probably contain hexaco-ordinated vanadium with a structure consisting of two octahedra sharing a common edge through alkoxide bridges. None of these compounds could be sublimed *in vacuo* without decomposition, and in each case a black residue with the general formula $V_2OCl_3(OR)_3$ remained after heating at 150°/0·1 mm. However, the vanadium showed no change in valency as a result of the decomposition. The vanadium oxychloride alkoxides $V_2OCl_3(OR)_3$ were insoluble in benzene but soluble in the parent alcohols from which they were recovered unchanged. In the case of the methoxide, ethoxide, and *iso*propoxide molecular weights in the boiling alcohols suggested the presence of only one vanadium atom per molecular unit on the average and it appears that the oxychloride alkoxides are dissociated by solvation. The reaction between alcohols and vanadium tetrachloride was extremely rapid and exothermic and had to be moderated in order to obtain the dichloride dialkoxide alcoholate free from oxychloride alkoxide. With *tert.*-butyl or *tert.*-amyl alcohols the dichloride dialkoxides could not be prepared by this method because of side reactions and the products obtained contained appreciable proportions of quinquevalent vanadium. However, the *tert.*-amyl derivative was obtained by alcohol interchange from the *iso*propoxide. Other dichloride dialkoxides were also prepared by this method to establish its generality and to emphasize that the reactivity of vanadium tetrachloride is confined to disubstitution.

[1] Bradley, Halim, and Wardlaw, *J.*, 1950, 3450.

XUM

Reactions of Molybdenum Pentachloride with Alcohols.—Molybdenum pentachloride reacts extremely vigorously with alcohols but under specially moderate conditions the reaction accords with: $MoCl_5 + 2ROH \longrightarrow MoCl_3(OR)_2 + 2HCl$; where R = Me or Et. The molybdenum trichloride dialkoxides are dimeric in boiling benzene; hence the molybdenum is probably hexaco-ordinated, with the dimer $Mo_2Cl_6(OR)_4$ consisting of two octahedra sharing a common edge through alkoxide bridges [cf. structure of $V_2Cl_4(OR)_4,2ROH$]. In view of the similar reactivity of titanium and vanadium tetrachlorides towards alcohols, a similarity was expected between niobium and molybdenum pentachlorides. However, niobium pentachloride forms [2] the dichloride trialkoxides $NbCl_2(OR)_3$ in contrast to the behaviour of molybdenum pentachloride. Moreover, there is a difference in behaviour towards *iso*propyl alcohol because, even under very mild conditions, the reaction involving molybdenum pentachloride produces a molybdenum oxychloride *iso*propoxide whereas niobium pentachloride forms the chloride *iso*propoxide. In fact it was not possible to prepare pure molybdenum trichloride di*iso*propoxide even by alcohol interchange involving the trichloride diethoxide, although the product was less hydrolysed than that obtained by direct reaction. On the other hand *n*-propyl alcohol exchanges with molybdenum trichloride diethoxide and forms the pure trichloride di-*n*-propoxide which is also dimeric in boiling benzene. This difference in behaviour of *n*- and *iso*-propyl alcohols is not surprising because it is a common feature of reactions involving metal chlorides and alcohols that hydrolytic side reactions occur when the alcohol has an alkyl group with a strong (+*I*) effect. We suggested that the side reaction was mainly caused by esterification of the alcohol by hydrochloric acid produced in the primary substitution reaction between metal chloride and alcohol.[3] However, the contrast in behaviour of niobium and molybdenum pentachlorides with *iso*propyl alcohol clearly reveals that the metal compound may also play a decisive rôle in the side reaction, perhaps as a catalyst for the esterification. Attempts to sublime the molybdenum trichloride dialkoxides *in vacuo* were unsuccessful owing to instability of the compounds. For example, prolonged heating of $MoCl_3(OEt)_2$ at 80°/0·1 mm. formed a molybdenum oxychloride ethoxide, soluble in benzene. At higher temperatures decomposition was more extensive but the products were still soluble in benzene until at 150°/0·1 mm. the product, approximating in composition to MoO_2Cl, was insoluble. The low average degrees of polymerisation (in benzene) of the oxychloride ethoxides suggest the presence of molybdenum–oxygen double bonds.

Experimental

All metal compounds described are extremely sensitive to hydrolysis and the usual special precautions [2] were taken to exclude moisture.

Vanadium Tetrachloride.—This was a viscous red liquid (Found: V, 26·3; Cl, 73·6. Calc. for VCl_4: V, 26·4; Cl, 73·6%) prepared by chlorination of vanadium at *ca.* 120° immediately prior to use.

Molybdenum Pentachloride.—The pure sublimed product (black crystals) was used as obtained commercially.

Analysis of Vanadium Compounds.—(a) *Vanadium.* The sample was dissolved in sulphuric acid (2N) and the quadrivalent vanadium titrated with standard permanganate after the addition of phosphoric acid (*ca.* 4 c.c.). Total vanadium was determined by reduction of a sample in sulphuric acid to the bivalent state in the Jones reductor. The solution from the reductor was passed directly into an excess of ferric alum solution and then titrated as before with permanganate. This procedure determined the percentage and valency of the vanadium.

(b) *Chloride.* The chloride was determined in nitric acid solution by Volhard's method.

(c) *Alkoxide.* Methoxide, ethoxide, or *iso*propoxide were determined by the chromic acid method,[1] which is unaffected by the presence of quadrivalent vanadium. In some cases carbon was determined by the Van Slyke method.[4]

[2] Bradley, Chakravarti, and Wardlaw, *J.*, 1956, 2381.
[3] Bradley, Halim, Sadek, and Wardlaw, *J.*, 1952, 2032.
[4] Multani, Ph.D. Thesis, London, 1956, 65.

XUM

TABLE 1. $VCl_2(OR)_2,ROH$.

R	VCl_4 (g.)	C_6H_6 (c.c.)	ROH (g.)	Product (g.)	Found (%) V	Cl	OR	C	Calc. (%) V	Cl	OR	C
Me	5·3	40	50	5·5	23·2	33·1	43·0	16·4	23·6	32·9	43·1	16·7
Et	4·8	50	46	6·3	19·1	29·0	51·9	—	19·7	27·6	52·3	—
Pr^n	6·1	50	41	9·2	17·2	23·8	—	36·1	17·0	23·7	—	36·3
Bu^n	4·0	40	45	7·0	14·8	21·2	—	41·8	14·9	20·8	—	42·2
n-Pentyl	3·0	25	29	5·85	13·4	18·7	—	—	13·2	18·4	—	—
Pr^i	5·3	36	55	8·2	16·9	23·7	57·9	36·1	17·0	23·7	59·0	36·3
Bu^i	4·0	40	35	7·1	14·9	21·6	—	41·6	14·9	20·8	—	42·2
Bu^s	3·0	32	20	5·3	14·7	21·0	—	39·8	14·9	20·8	—	42·2
Bu^t	4·8	24	35	6·9	16·0 *	22·6	—	—	14·9	20·8	—	—
Am^t	5·1	40	30	9·3	14·1 †	20·3	—	9·4	13·3	18·5	—	47

* V^{IV} = 9·0%. † V^{IV} = 7·8%. In all other cases V (total) = V^{IV}.

TABLE 2. $VCl_2(OR)_2,ROH$.

R	Sample (g.)	$V_2OCl_3(OR)_3$ (g.)	Mol. wt. Found	Mol. wt. Calc.	Analysis Found (%) V	Cl	OR	C	Calc. (%) V	Cl	OR	C
Me	10·0	7·4	164·2	317·5	31·4	33·1	27·2	—	32·1	33·5	29·2	—
Et	8·6	6·5	186·8	359·5	27·8	29·4	35·5	—	28·3	29·6	37·5	—
Pr^i	10·0	6·5	203	401·5	25·1	27·3	43·9	—	25·4	26·5	44·1	—
Pr^n	8·0	5·3	—	—	25·3	27·8	—	26·6	25·4	26·5	—	26·9

TABLE 4.

Starting material (g.)	C_6H_6 (c.c.)	ROH (g.)	Product (g.)	Found (%) M	Cl	OR	C	Calc. (%) M	Cl	OR	C
$VCl_2(OEt)_2,EtOH$ (4·2)	—	Pr^iOH (225)	$VCl_2(OPr^i)_2,Pr^iOH$ (4·9)	16·8	23·8	57·9	—	17·0	23·7	59·0	—
$VCl_2(OPr^i)_2,Pr^iOH$ (5·0)	80	Pr^nOH (60)	$VCl_2(OPr^n)OH$ (5·0)	17·2	24·0	—	36·4	17·0	23·7	—	36·3
,, (3·0)	—	MeOH (120)	$VCl_2(OMe)_2,MeOH$ (2·1)	23·7	33·2	42·9	—	23·6	32·9	43·1	—
,, (4·2)	50	Bu^tOH (4·3)	$VCl_2(OBu^t)_2Bu^tOH$ (4·5)	24·1 *	23·8	—	12·1	14·9	20·8	—	42·2
$VCl_2(OEt)_2,EtOH$ (4·0)	50	,, (4·0)	,, (4·0)	23·2 †	24·1	—	11·8	14·9	20·8	—	42·2
,, (4·8)	40	Am^tOH (4·9) ‡	$VCl_2(OAm^t)_2,Am^tOH$ (7·1)	13·5	19·0	—	44·8	13·3	18·5	—	47·0
$VCl_2(OPr^i)_2,Pr^iOH$ (3·0)	32	,, (2·7)	,, (3·8)	13·7	18·9	—	46·0	13·3	18·5	—	47·0
$MoCl_3(OEt)_2$ (3·0) ...	80	Pr^nOH (25)	$MoCl_3(OPr^n)_3$ (3·3)	29·7	33·3	—	21·6	29·9	33·1	—	22·4
,, (3·0)	—	Pr^iOH (75)	$MoCl_3(OPr^i)_3$ (3·0)	33·4	32·1	32·0	—	29·9	33·1	36·9	—

* V^{IV} = 19·3%. † V^{IV} = 19·2%; in all other cases V (total) = V^{IV} and Mo (total) = Mo^V. ‡ Am^t = *tert.*-amyl.

TABLE 3.

R	ROH (g.)	$MoCl_5$ (g.)	$MoCl_3(OR)_2$ (g.)	Found (%) Mo	Cl	OR	C	Calc. (%) Mo	Cl	OR	C
Me ...	50	5·0	4·8	35·9	40·7	23·5	—	36·2	40·2	23·4	—
Et ...	75	5·0	5·5	32·1	37·8	30·9	16·3	32·8	36·4	30·8	16·4
Pr^i ...	75	5·0	6·0	40·9	27·8	21·9	—	29·9	33·1	36·9	—

TABLE 5.

Compound	Range of *m* (g.)	C_6H_6 (g.)	$\Delta T/m$ (°c/g.)	Mol. wt. Found	Calc.
$VCl_3(OEt)_2$,EtOH	0·0352—0·2948	17·25	0·325	525	258
$VCl_3(OPr^i)_2$,Pr^iOH	0·0318—0·3721	16·80	0·287	611	300
$MoCl_3(OMe)_2$	0·1412—0·4162	19·00	0·288	539	264·5
$MoCl_3(OEt)_2$	0·0862—0·3215	17·80	0·274	604	292·5
$MoCl_3(OPr^n)_2$	0·0521—0·3200	16·80	0·257	683	320·5

Analysis of Molybdenum Compounds.—(a) *Molybdenum.* Generally, molybdenum was determined volumetrically similarly to vanadium. Some analyses were checked and confirmed by the α-benzoin oxime method, but the method involving the precipitation of molybdenum sulphide was found unsuitable because it gave significantly low results.

(b) *Chloride.* The chloride was determined volumetrically by Volhard's method after we found that the gravimetric method (silver chloride) on the filtrate following the removal of molybdenum as sulphide gave the same result.

(c) *Alkoxide.* The chromic acid method was used for methoxide, ethoxide, and *iso*propoxide. However, it was necessary to allow for the chromic acid used in oxidising the molybdenum to the sexavalent state. Some carbon determinations were also made by the Van Slyke method.[4]

Reactions involving Vanadium Tetrachloride.—Vanadium tetrachloride was dissolved in benzene and the solution was cooled to *ca.* −78°. The alcohol was then added dropwise, causing a vigorous reaction. The solution was then evaporated to dryness under reduced pressure. This procedure was adopted throughout and the details are given in Table 1.

All of the vanadium dichloride dialkoxide alcoholates were green solids which were very soluble in alcohol or benzene, and attempts to recrystallise them were unsuccessful. In each experiment the volatile products, trapped (at −78°) during the evaporation of solvent, were yellow and contained traces of chloride and quinquevalent vanadium in the atomic ratio of 3 : 1, suggesting the presence of $VOCl_3$.

Action of Heat on Vanadium Dichloride Dialkoxide Alcoholates.—Each compound was heated at 150°/0·1 mm. until no more volatile products were condensed at *ca.* −78°. The residue was in each case black. Results are given in Table 2. The molecular weights were determined ebullioscopically in the parent alcohols.

The experiment was repeated several times on the dichloride diethoxide ethyl alcoholate but the black residue always had the composition $V_2OCl_3(OEt)_3$. The product was soluble in ethyl alcohol and the solution gave on evaporation of the solvent a *green* solid still having the composition $V_2OCl_3(OEt)_3$ (Found: V, 27·9; Cl, 29·3; OEt, 37·1. Calc. for $C_6H_{15}O_4Cl_3V_2$: V, 28·3; Cl, 29·6; OEt, 37·5%). At 250°/0·1 mm. further decomposition occurred and the black residue (Found: V, 34·4; Cl, 29·8; OEt, 27·8%) was insoluble in alcohol. In all these experiments traces of $VOCl_3$ were detected in the volatile products but the vanadium in the non-volatile residue was entirely quadrivalent.

Reactions involving Molybdenum Pentachloride.—The pentachloride, added cautiously to the cold (*ca.* −78°) alcohol, caused a vigorous reaction. The excess of alcohol was then removed under reduced pressure and left a brown solid. The results are given in Table 3. In each case all the molybdenum in the product was quinquevalent.

Alcohol-interchange Reactions.—The chloride alkoxide was usually dissolved in a mixture of benzene and the higher alcohol. The solution was then fractionally distilled until the lower alcohol was completely removed. When vanadium dichloride dimethoxide was prepared the fractional distillation was omitted for obvious reasons. The results are given in Table 4.

Action of Heat on Molybdenum Trichloride Diethoxide.—(a) *At* 80°. A sample was heated in a molecular still at 0·1 mm. until no more volatile products were trapped at *ca.* −78°. The compound did not sublime and analysis of the non-volatile residue (Found: Mo, 36·5; Cl, 33·2; OEt, 26·0%; *M*, 807) showed that decomposition had occurred. The residue was

soluble in benzene and a molecular-weight determination in this solvent showed an average degree of polymerisation of 3·1.

(b) *At* 140°. The residue obtained similarly at 140°/0·05 mm. was further decomposed (Found: Mo, 49·4; Cl, 21·4; OEt, 15·6%; *M*, 1387) and had an average degree of polymerisation of 7·2 in boiling benzene.

(c) *At* 150°. Prolonged heating at 150°/0·05 mm. gave a residue which was insoluble in benzene (Found: Mo, 56·2; Cl, 20·2; OEt, 7·7%).

Molecular-weights.—These were determined ebullioscopically over a range of concentrations in the apparatus previously described.[2] The results are given in Table 5.

BIRKBECK COLLEGE, MALET STREET, LONDON, W.C.1. [*Received, August 22nd,* 1958.]

---

937. *Chloroalkoxides of Titanium, Zirconium, Cerium, and Thorium.*

By D. C. BRADLEY, R. N. P. SINHA, and W. WARDLAW.

Various methods for preparing metal chloroalkoxides have been explored, including reactions involving a chloroalcohol, chloroaldehyde or a chloroalkyl carboxylate. The following new compounds were prepared: $Ti(OX)_4$; $Zr(OX)_4$; $Ce(OX)_4.C_5H_5N$; $Th(OX)_4.2C_5H_5N$; $TiCl(OX)_3$; $ZrCl(OX)_3$; $Ti(OEt)(OX)_3$; $Ti(OPr^i)(OX)_3$; $Ti(OY)_4$; $Zr(OY)_4.2Me_2CO$ and $Ti(OZ)_4$, where $X = CCl_3{\cdot}CMe_2$, $Y = CCl_3{\cdot}CH_2$, and $Z = CH_2Cl{\cdot}CH_2$. These results throw more light on the mechanism of the reaction of alcohols with metal chlorides and on the structural theory for polymeric metal alkoxides.

A MAJOR problem in interpreting the effect of the alkyl group on the properties of metal alkoxides has been to distinguish between steric and electronic effects.[1,2] The evidence supporting our view [2] that steric effects predominate is based on the behaviour of a large number of different alkoxides but in particular it turns on the behaviour of the *neo*pentyloxide group. Although the remarkable steric effect of the *neo*pentyl group is well established,[3] there still remains the possibility of transmission of a small amount of the $+I$ inductive effect of the *tert.*-butyl group through the alcoholic carbon. In view of the similarity of the size of the methyl group to that of covalently bound chlorine it seemed likely that suitably chosen chloroalkyl groups would provide a decisive means of testing our theory. For example, the 2 : 2 : 2-trichloroethoxide group will resemble the *neo*pentyloxide group in steric effect but has the opposite electronic inductive effect. This paper deals with the chloroalkoxides of titanium, zirconium, cerium(IV), and thorium; introduction of chlorine into the alkyl group caused some unexpected results.

Tetrakis-1-methyl-1-trichloromethylethoxy-derivatives.—The tetrakis-1-methyl-1-trichloromethylethoxy-derivatives of titanium and zirconium were obtained by alcohol interchange of 1-methyl-1-trichloromethylethanol ("chlorbutol") and the metal *iso*propoxide. Both compounds were monomeric in boiling benzene and the titanium derivative sublimed at 150°/0·15 mm. whilst the zirconium derivative decomposed above *ca.* 130°/0·1 mm. Attempts to prepare the cerium(IV) and thorium derivatives by the same method were unsuccessful, being accompanied by precipitation of decomposition products. In the case of thorium this may be due to the basic character of the *iso*propoxide. However, further work showed that the titanium and zirconium derivatives could also be prepared by the ammonia method involving either the metal chloride [1] or dipyridinium zirconium hexachloride.[4] When the ammonia method was tried with either the complex chlorocerate or the complex chlorothorate, $Ce(O{\cdot}C_4H_6Cl_3)_4.C_5H_5N$ and

[1] Bradley and Wardlaw, *J.*, 1951, 280.
[2] Bradley, Mehrotra, and Wardlaw, *J.*, 1952, 2027.
[3] Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173.
[4] Bradley, Halim, Sadek, and Wardlaw, *J.*, 1952, 2032.

XUM

$Th(O{\cdot}C_4H_6Cl_3)_4,2C_5H_5N$ respectively were obtained. Neither compound could be obtained free from addended pyridine and both decomposed at *ca.* 115—120°/0·1 mm. These results show that the presence of chlorine in a tertiary alcohol profoundly affects the reactivity of the alcohol. For example, previous work involving reactions of tertiary alcohols with either the complex zirconium [4] or cerium [5] chlorides in the presence of ammonia showed that chloride alkoxide pyridine adducts $MCl(OR)_3,C_5H_5N$, where M = Zr or Ce^{IV}, were formed. Yet with chlorbutol complete replacement of metal–chlorine bonds occurs. Now, we have found that chlorbutol reacts with either titanium or zirconium tetrachlorides forming the tris-1-methyl-1-trichloromethylethoxy-metal monochlorides $MCl(O{\cdot}C_4H_6Cl_3)_3$, where M = Ti or Zr. The titanium compound was caused to react with ethanol or *iso*propyl alcohol and ammonia and formed the mono-ethoxide and mono*iso*propoxide respectively. It is noteworthy that normal alcohols react with these tetrachlorides to form respectively $TiCl_2(OR)_2$,ROH and a mixture of $ZrCl_3(OR)$,ROH and $ZrCl_2(OR)_2$,ROH, but tertiary alcohols are involved in a more complex reaction which results in the hydrolysis of the metal compounds. This contrast in behaviour between chlorbutol and unsubstituted tertiary alcohols in their reactions with metal chlorides shows clearly the influence of the electronic effects of the alkyl groups on the reactivity of alcohols with metal chlorides. In an earlier paper [6] we suggested that part of the " driving force " for the reaction between metal chloride and an alcohol is the induced positive charge (δ+) on the metal caused by the electronegative chlorine atoms (*viz.*, $\overset{\delta+}{M}\text{–}\overset{\delta-}{Cl}$), and that replacement of the chlorine by the less electronegative alkoxide groups reduces this driving force and ultimately prevents further replacement. The behaviour of chlorbutol agrees with this hypothesis because the (−*I*) effect of the trichloromethyl group makes the 1-methyl-1-trichloromethyl-ethoxide group more electronegative than a normal alkoxide group and the (δ+) on the metal is sustained through a greater degree of replacement of M–Cl bonds.

From the steric viewpoint the 1-methyl-1-trichloromethylethoxide group resembles the 1 : 1 : 2 : 2-tetramethylpropoxide group and it is noteworthy that the volatilities of the titanium derivatives of the former (150°/0·15 mm.) and the latter (163°/0·5 mm.) are very similar and both compounds are monomeric.

Tetrakis-2 : 2 : 2-*trichloroethoxy-derivatives*.—To explore the scope of preparative methods for metal chloroalkoxides we tried the Meerwein–Ponndorf–Verley reaction of 1 : 1 : 1-trichloroacetaldehyde (" chloral ") with the metal alkoxides. With titanium *iso*propoxide the following reaction occurred:

$$Ti(OPr^i)_4 + 4Cl_3C{\cdot}CHO \longrightarrow Ti(O{\cdot}CH_2{\cdot}CCl_3)_4 + 4Me_2CO$$

The titanium tetrakis-2 : 2 : 2-trichloroethoxide had a degree of polymerisation of 1·5, close to that (1·3) for titanium tetra*neo*pentyloxide, in boiling benzene. This clearly emphasises the major importance of steric effects in the influence of chain-branching on physicochemical properties of the metal alkoxides. Thus the similar size and shape of the 2 : 2 : 2-trichloroethoxide and *neo*pentyloxide groups means that from steric considerations alone their titanium derivatives should have the same degree of polymerisation. On the other hand the −*I* inductive effect of the trichloromethyl group compared with the +*I* effect of the *tert.*-butyl group causes the 2 : 2 : 2-trichloroethoxide group to be more electronegative than the *neo*pentyloxide group, and the titanium derivative of the former will have a higher (δ+) than that of the latter. The derivative with the higher (δ+) on its titanium atom will have the greater tendency to polymerise through intermolecular bonding. When zirconium *iso*propoxide was treated with chloral under similar conditions half of the acetone produced in the reaction was retained by co-ordination with the zirconium in the compound $Zr(O{\cdot}CH_2{\cdot}CCl_3)_4,2Me_2CO$. Attempts to remove the acetone

[5] Bradley, Chatterjee, and Wardlaw, *J.*, 1957, 2600.
[6] Bradley, Halim, and Wardlaw, *J.*, 1950, 3450.

were unsuccessful owing to decomposition of the compound at 100°/0·1 mm. This compound is of special interest because it is another example of a co-ordination compound involving a zirconium alkoxide. These are rare because the metal alkoxide prefers to co-ordinate through an alkoxide group from a neighbouring molecule to form a polymer. In fact most attempts to form co-ordination compounds with zirconium alkoxides have failed. Even zirconium tetra*iso*propoxide, which co-ordinates with pyridine or *iso*propyl alcohol, would not co-ordinate with diethyl ether, triethylamine, thiourea, ethylenediamine, or αα′-dipyridyl. However, the tetrachloride, trichloride monoethoxide, dichloride diethoxide, dichloride di*iso*propoxide, or monochloride tri*iso*propoxide of zirconium forms some stable complexes and it appears that the combination of an electronegative group with the zirconium is a necessity for complex formation. This may well explain the behaviour of zirconium tetrakis-2 : 2 : 2-trichloroethoxide. When either cerium(IV) or thorium *iso*propoxide was treated with chloral the Meerwein–Ponndorf–Verley reaction was complicated by side reactions and the tetrakis-2 : 2 : 2-trichloroethoxides could not be obtained. In the case of thorium this may be due to the basic character of thorium *iso*propoxide.

Tetrakis-2-chloroethoxy-derivatives.—Since metal alkoxides undergo transesterification with organic esters it seemed worth while to try to prepare a chloroalkoxide by this method. Titanium tetra*iso*propoxide reacted with 2-chloroethyl acetate according to the equation:

$$Ti(OPr^i)_4 + 4CH_3{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2Cl \longrightarrow Ti(O{\cdot}CH_2{\cdot}CH_2Cl)_4 + 4CH_3{\cdot}CO_2Pr^i$$

However, zirconium *iso*propoxide appeared not to react at a significant rate with 2-chloroethyl acetate.

Experimental

Materials.—The complex chlorides and the *iso*propoxides of titanium, zirconium, cerium(IV), and thorium were prepared by the methods already described.[2, 4, 7, 8] "Chlorbutol" and 2-chloroethyl acetate were dried azeotropically with benzene containing *ca.* 3% of *iso*propyl alcohol. Chloral was shaken with sulphuric acid (conc.), separated, and then distilled. Special precautions were taken throughout to avoid hydrolysis and reactions were conducted in an atmosphere of oxygen-free nitrogen. Analyses and molecular-weight determinations were carried out as described previously.[2, 4, 7, 8]

Reactions of Titanium Tetrachloride or Zirconium Tetrachloride with "Chlorbutol."—Chlorbutol (55 g.), added to titanium tetrachloride (12 g.) in carbon tetrachloride (200 c.c.), caused a vigorous reaction. After 8 hours' refluxing, the volatile products and solvent were evaporated off, leaving *tris*-1-*methyl*-1-*trichloromethylethoxytitanium monochloride* as a white solid (34 g.) [Found: Ti, 7·86%; *M*, 611·8. $TiCl(OC_4H_6Cl_3)_3$ requires Ti, 7·82%; *M*, 612·9]. From a similar reaction of the tetrachloride (11 g.) and chlorbutol (50 g.) in benzene (200 c.c.), the product (30 g.) had the analysis: Ti, 8·1; C, 23·4; H, 3·39; Cl, 61. $TiCl(OC_4H_6Cl_3)_3$ requires Ti, 7·82; C, 23·5; H, 2·94; Cl, 57·9%. A sample of the foregoing product heated in a short-path still sublimed at 105—110°/0·1 mm. (Found for the sublimate: Ti, 7·85%). The compound (12 g.) in carbon tetrachloride (250 c.c.) was treated with ethanol (1·0 g.) and ammonia. Ammonium chloride was filtered off and the filtrate on evaporation under reduced pressure left a white solid (11·8) [Found: Ti, 7·65; EtO, 7·08%; *M*, 635. $Ti(OEt)(OC_4H_6Cl_3)_3$ requires Ti, 7·69; EtO, 7·23%; *M*, 622·4]. *Tris*-1-*methyl*-1-*trichloromethylethoxytitanium monoethoxide* sublimed at 160°/0·1 mm. (Found for the sublimate: Ti, 7·68%). Similarly, *tris*-1-*methyl*-1-*trichloromethylethoxytitanium monoiso*propoxide was obtained from the reaction involving the monochloride (10 g.), *iso*propyl alcohol (0·995 g.), and ammonia in carbon tetrachloride (250 c.c.) as a gum (8 g.) [Found: Ti, 7·53; Pr^iO, 8·60%; *M*, 640. $Ti(OPr^i)(OC_4H_6Cl_3)_3$ requires Ti, 7·53; Pr^iO, 9·27%; *M*, 636·4]. The mono*iso*propoxide gave volatile products at 125°/0·1 mm. but the condensate (Found: Ti, 8·2%) was not the mono*iso*propoxide. "Chlorbutol" (38 g.), added to a suspension of zirconium tetrachloride (10 g.) in benzene (200 c.c.), caused a vigorous reaction with evolution of hydrogen chloride. After 9 hours' refluxing the volatile

[7] Bradley, Chatterjee, and Wardlaw, *J.*, 1956, 2260.
[8] Bradley, Saad, and Wardlaw, *J.*, 1954, 1091.

products and solvent were evaporated off under reduced pressure and left a gum (24 g.) [Found: Zr, 14·1%; *M*, 651. $ZrCl(OC_4H_6Cl_3)_3$ requires Zr, 13·9%; *M*, 656].

Reactions involving Chlorbutol, Metal Chlorides, and Ammonia.—These were conducted by our standard procedures and the results are in Table 1.

Reactions of Chlorbutol with Metal iso*Propoxides.*—Chlorbutol was added to the benzene solution of the metal *iso*propoxide and the liberated *iso*propyl alcohol was removed by azeotropic fractionation. The solvent was then evaporated off under reduced pressure. The results are in Table 2.

TABLE 1.

Metal chloride taken	Chlorbutol (g.)	Benzene (c.c.)	Product	Analysis: Found	Analysis: Calc.
$TiCl_4$ (11 g.)	50	200	$Ti(OC_4H_6Cl_3)_4$ (35 g.)	Ti, 6·37%; *M*, 760	Ti, 6·35%; *M*, 754
$ZrCl_4$ (8 g.)	35	200	$Zr(OC_4H_6Cl_3)_4$ (20 g.)	Zr, 11·3; C, 24·2; H, 3·92; Cl, 52·0%; *M*, 802	Zr, 11·4; C, 24·1; H, 3·01; Cl, 53·4%; *M*, 797
$(C_5H_6N)_2ZrCl_6$ (10 g.)	25	250	$Zr(OC_4H_6Cl_3)_4$ (10·5 g.)	Zr, 11·2%	Zr, 11·4%
$(C_5H_6N)_2CeCl_6$ (12 g.)	25	200	$Ce(OC_4H_6Cl_3)_4.C_5H_5N$ (14 g.)	Ce, 15·3; C, 29·5; H, 3·3%	Ce, 15·15; C, 27·2; H, 3·1%
$(C_5H_6N)_2ZrCl_6$ (8 g.)	20	200	$Th(OC_4H_6Cl_3)_4.2C_5H_5N$ (10 g.)	Th, 21·4; C, 28·3; H, 3·67; Cl, 37·9; N, 2·0%	Th, 21·2; C, 28·5; H, 3·1; Cl, 38·8; N, 2·5%

TABLE 2.

Metal *iso*propoxide taken	Chlorbutol (g.)	Benzene (c.c.)	Product (g.)	Analysis: Found	Analysis: Calc.*
$Ti(OPr^i)_4$ (10 g.)	30·0	250	20·5	Ti, 6·36%; *M*, 755	Ti, 6·35%; *M*, 754
$Zr(OPr^i)_4.Pr^iOH$ (7 g.) ...	20·0	250	12	Zr, 11·5%; *M*, 798	Zr, 11·4%; *M*, 797
$Ce(OPr^i)_4.Pr^iOH$ (8 g.) ...	18·5	250	6·0	Ce, 41·9%	Ce, 16·5%
$Th(OPr^i)_4$ (8 g.)	25·0	250	9·0	Th, 39·0%	Th, 24·7%

* Calc. for metal tetrakis-2 : 2 : 2-trichloroethoxide.

Titanium Tetrakis-2 : 2 : 2-trichloroethoxide.—Chloral (18 g.) was added to titanium *iso*propoxide (8 g.) in benzene (200 c.c.). The mixture was fractionally distilled until no more acetone was collected and the solvent was then evaporated off under reduced pressure leaving a solid (15 g.) [Found: Ti, 7·60%; *M*, 962·5. $Ti(OC_2H_2Cl_3)_4$ requires Ti, 7·50%; *M*, 642]. Attempts to sublime the *compound* led to decomposition (Found for the residue: Ti, 9·65%).

Bisacetone Adduct of Zirconium Tetrakis-2 : 2 : 2-trichloroethoxide.—Chloral (20 g.) and zirconium tetra*iso*propoxide (10 g.) in benzene (200 c.c.) were fractionally distilled until the liberation of acetone ceased. Removal of solvent under reduced pressure left a solid (18 g.) [Found: Zr, 11·5; C, 21·0; H, 2·2; Cl, 55·0. $Zr(OC_2H_2Cl_3)_4.2Me_2CO$ requires Zr, 11·4; C, 21·0; H, 2·5; Cl, 53·2%]. The *compound* retained its addenda up to 100°/0·1 mm. (Found: Zr, 11·8%) but did not sublime. The presence of acetone was proved by treating a sample with sulphuric acid (2N) and testing the distillate with 2 : 4-dinitrophenylhydrazine.

Titanium Tetrakis-2-chloroethoxide.—Titanium *iso*propoxide (10 g.) and 2-chloroethyl acetate (20 g.) were caused to react in boiling benzene (250 c.c.). Fractional distillation was carried out until no more *iso*propyl acetate was liberated. Evaporation of the solvent under reduced pressure left a viscous liquid (11·3 g.) [Found: Ti, 13·0. $Ti(CO_2H_4Cl)_4$ requires Ti, 13·2%]. In a similar reaction of zirconium *iso*propoxide with 2-chloroethyl acetate no *iso*propyl acetate was detected after prolonged fractional distillation and the zirconium compound (Found: Zr, 25·4%) which was recovered from solution was not the tetrakis-2-chloroethoxide.

*Addition of Donor Molecules to Zirconium Tetrais*o*propoxide.*—In separate experiments diethyl ether, triethylamine, thiourea, ethylenediamine, and αα′-dipyridyl were added to zirconium tetra*iso*propoxide in benzene in the molar ratio of 4 : 1 respectively. No crystalline products were formed and evaporation of the solutions under reduced pressure left the tetra-*iso*propoxide in each case.

We thank Peter Spence and Sons Ltd. for a gift of titanium tetrachloride.

BIRKBECK COLLEGE, MALET STREET, LONDON, W.C.1. [*Received, August 22nd,* 1958.]

XUM

938. *The Chemistry of Uranyl Acetylacetone Complex.*

By Alan E. Comyns, Bryan M. Gatehouse, and Eric Wait.

Three crystalline modifications of uranyl acetylacetone monohydrate have been prepared and their unit-cell parameters, infrared spectra, visible spectra, and magnetic susceptibilities studied. Crystalline solvates of uranyl acetylacetone have also been prepared with ethanol, dioxan, acetylacetone, and acetophenone.

The visible and ultraviolet spectra of solutions of anhydrous uranyl acetylacetone in ethanol and in benzene are presented; the compound is dimeric in benzene at 80°.

The electrical conductivities of aqueous solutions of uranyl acetylacetone have been measured: at 0·2° the solutions are relatively stable and the equivalent conductivity is approximately unity at 10^{-4}M; at 25° the solutions are rapidly hydrolysed with deposition of $UO_3,2H_2O$.

Many co-ordination compounds of the uranyl ion have been prepared,[1] but none has been studied in sufficient detail to enable even the co-ordination number of the uranium atom to be determined. The visible and ultraviolet absorption spectra of solutions of the uranyl complexes of several aromatic β-diketones have been examined by Sacconi and Giannoni,[2] who conclude that in these compounds the co-ordination number of the uranium atoms exceeds six. Uranyl acetylacetone monohydrate was prepared first by Biltz and Clinch,[3] and more recently by Gilman and his co-workers.[4] Abrahamson and Brown [5] and Schlesinger and his co-workers [6] have prepared the anhydrous compound.

We prepared uranyl acetylacetone monohydrate by the slow addition of aqueous sodium hydroxide to warm aqueous solutions containing equivalent quantities of uranyl nitrate and acetylacetone. The crystals which formed when these solutions cooled under apparently identical conditions assumed a wide variety of habits; seeding was of major importance. They were examined by optical and *X*-ray crystallography and had three main crystalline forms, two of which (forms 1 and 2) were yellow and one (form 3) was red. Photographs of typical preparations are given in the Plate.

Form 3 was unstable, changing spontaneously into form 2. Some preparations of form 3 started to change colour within a few hours of preparation, whereas one was still unchanged after two years: samples kept at *ca.* 4° remained unchanged indefinitely. Observations with a polarising microscope showed that when a red crystal had changed into the yellow form the shape was at first unchanged but the " crystal " was granular and microcrystalline. After several months at room temperature the " crystal " became macrocrystalline and the outline was distorted by the new crystal faces. In one preparation there was no distortion of the crystals; they slowly changed into yellow single crystals while maintaining their original form, but they now showed oblique extinction. Oscillation photographs of one of these new yellow crystals showed it to be of form 2, and this was also shown by *X*-ray powder photographs and the infrared spectrum of this material.

Crystals of form 1 became opaque on long exposure to the atmosphere, and *X*-ray powder photographs showed that they had changed into $UO_3,2H_2O$.

When crystals of form 3 were immersed in dichloroethane at room temperature they dissolved, crystals of form 1 being formed simultaneously. When the dichloroethane was initially saturated with respect to form 1 these new crystals developed on the faces of the

[1] Croxton, " Uranium and its Compounds; a Bibliography of Unclassified Literature," U.S.A.E.C. report K-295, part 2 (1951); Allen, supplement to same, T.I.D. 3041 (1953); Comyns, " The Co-ordination Chemistry of Uranium: a Critical Review," A.E.R.E. report C/R 2320 (1957).

[2] Sacconi and Giannoni, *J.*, 1954, 2368, 2751.

[3] Biltz and Clinch, *Z. anorg. Chem.*, 1904, **40**, 218.

[4] Gilman, Jones, Bindschadler, Blume, Karmas, Martin, Nobis, Thirtle, Yale, and Yoeman, *J. Amer. Chem. Soc.*, 1956, **78**, 2790.

[5] Abrahamson and Brown, *ibid.*, 1950, **72**, 1424.

[6] Schlesinger, Brown, Katz, Archer, and Lad, *ibid.*, 1953, **75**, 2446.

XUM

form 3 crystals; this process is shown in the Plate. Recrystallisation of crystals of form 1 from warm dichloroethane gave well-developed crystals of form 1, although some precipitation of a hydrolysis product (probably $UO_3,2H_2O$) occurred if the solution was kept warm for too long.

Crystal Data.—Form 1. Two closely-related modifications of this form occurred together, both in batches prepared from aqueous solution and in those crystallised from dichloroethane. Form 1*A* is orthorhombic, elongated along [010], with $a = 16{\cdot}72 \pm 0{\cdot}05$, $b = 7{\cdot}06 \pm 0{\cdot}01$, $c = 48{\cdot}5 \pm 0{\cdot}1$ Å. The calculated density, 16 molecules being assumed per unit-cell, is 2·26 g./c.c. Form 1*B* is monoclinic, elongated along [010], with $a = 16{\cdot}64 \pm 0{\cdot}05$, $b = 7{\cdot}06 \pm 0{\cdot}01$, $c = 12{\cdot}92 \pm 0{\cdot}05$ Å, $\beta = 109{\cdot}0° \pm 0{\cdot}5°$. The calculated density, 4 molecules being assumed per unit-cell, is 2·25 g./c.c. The observed density, for a sample consisting of a mixture of both forms, was 2·26 g./c.c. The geometrical relation between the two unit-cells is approximately as shown in Fig. 1, but careful comparison of the two modifications showed that the spacing along [001] in form *A* is less than four times that in form *B*.

FIG. 1. *Relation between the orthorhombic unit-cell of form 1A, and the monoclinic unit-cell of form 1B. The a-dimensions (not shown) are identical.*

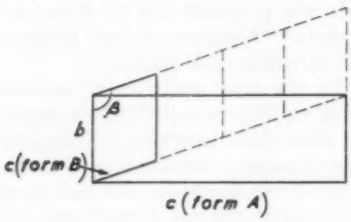
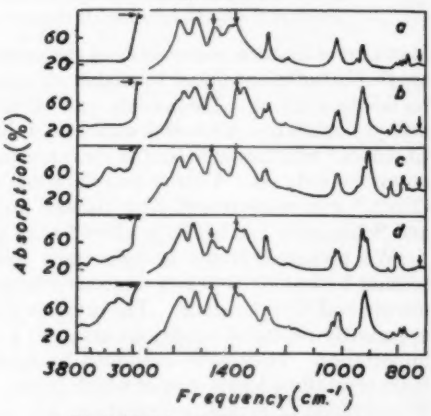


FIG. 2. *Infrared spectra of thorium and uranyl acetylacetones.*



a, $Th(C_5H_7O_2)_4$; *b*, $UO_2(C_5H_7O_2)_2$; *c*, $UO_2(C_5H_7O_2)_2,H_2O$, form 3; *d*, $UO_2(C_5H_7O_2)_2,H_2O$, form 2; *e*, $UO_2(C_5H_7O_2)_2,H_2O$, form 1. Nujol bands are marked by arrows.

In form 1*B* all *X*-ray reflections of the class *hkl* with *l* odd were observed as streaks rather than spots. This indicates a disordered structure, which will be described in detail elsewhere.

Form 2. Two monoclinic habits were observed: rectangular tablets, elongated along [010], showing straight extinction; and prisms, elongated along [100], with oblique extinction: the optic sign was negative. The cell-dimensions were: $a = 7{\cdot}825 \pm 0{\cdot}010$, $b = 11{\cdot}98 \pm 0{\cdot}01$, $c = 15{\cdot}65 \pm 0{\cdot}02$ Å, $\beta = 103{\cdot}7° \pm 0{\cdot}3°$, and the space-group $P2_1/c$. The calculated density, 4 molecules being assumed per unit-cell, is 2·27 g./c.c.; that observed was 2·24 g./c.c.

Form 3. This occurred as orthorhombic red needles, elongated along [001], showing straight extinction: the optic sign was negative. The cell-dimensions were: $a = 25{\cdot}46 \pm 0{\cdot}10$, $b = 12{\cdot}95 \pm 0{\cdot}05$, $c = 8{\cdot}92 \pm 0{\cdot}05$ Å, and the space-group *Pccn*. The calculated density, 8 molecules being assumed per unit-cell, is 2·20 g./c.c.; that observed was 2·22 g./c.c.

Infrared Spectra.—Infrared spectra of the three monohydrates and the anhydrous

XUM

Form 1 (× 18)

Form 3 (× 23)

Form 2 (× 20)

Form 2 (× 20)

(*a*) (*b*) (*c*)

Form **3** (× **23**) in saturated dichloroethane:

(*a*) After ½ min. (*b*) After 2 min. (*c*) After 18 min.

Crystals of uranyl acetylacetone monohydrate.

[*To face p.* **4656**.

XUM

form of uranyl acetylacetone, and of thorium acetylacetone, are shown in Fig. 2, and the frequencies of the bands are given in the Table. No absorption band was observed between 2860 and 1700 cm.$^{-1}$. The spectra of the anhydrous forms derived from all three monohydrates were almost identical. The spectrum of the yellow monohydrate obtained by spontaneous transformation of the red monohydrate (form 3) at room temperature was found to be almost identical with that of the monohydrate of form 2.

Bands due to water. Thorium acetylacetone and anhydrous uranyl acetylacetone showed no absorption band in the 3000 cm.$^{-1}$ or the 1640 cm.$^{-1}$ region. All three monohydrates of uranyl acetylacetone exhibited a shoulder or a peak at *ca.* 1640 cm.$^{-1}$, characteristic of the bending vibration of the water molecule, and also a pair of broad bands in the region 3000—3400 cm.$^{-1}$, characteristic of the two stretching vibrations of the water molecule. In addition, form 2 of the monohydrate exhibited a weak but sharp peak at 3580 cm.$^{-1}$. This peak could be due to hydroxyl groups either attached to uranium or in the form of enolic acetylacetone, but it is more probably due to a complex splitting of the O–H stretching vibrations of water molecules. Similar spectra in this region are given by some hydrated metal halides [7] and by hydrated cyclic metaphosphates.[8]

Infrared absorption frequencies of uranyl and thorium acetylacetones.

Uranyl acetylacetone							Thorium acetyl-acetone
Form 1 hydrate	Form 2 hydrate	Form 3 hydrate	Form 3 trans.	Form 1 anhyd.	Form 2 anhyd.	Form 3 anhyd.	
		761					765
		(774)					
780		781		777	778	778	779
793	799		799				792
	805		805				805
814				816	816	816	
		825					
	835	830	836	837	838	837	
					(903)		
	912	918	910	(912)	(910)	914	923
917	925	905	924	924	925	926	
(943)		(942)	(947)				943
1012	1014	1017	1014	1012	1014	1019	1018
	1024		1022	1022	1024	1024	
(1032)	(1031)		(1032)				
		1176	1171	1172		1172	
1195	1198	1190	1200	1200	1200	1200	1193
1271	1272	1272	1276	1264	1264	1264	1267
		(1280)		1279	1277	1279	
1361	1348	(1370)	1348	1350	1351	1351	1401
(1431)	1427	1431	1433	(1437)	(1437)	1435	
1524	1531	1534	1531	1531	1529	1529	1531
1572	1572	1580	1577	1575	1570	1567	1585
1577							
				1592	(1590)	(1590)	
(1650)	(1637)	1647	1639				
3205	(3090)	3205	×				
(3320)	3255	3362	×				
	3580		×				

Units, cm.$^{-1}$. Approximate positions of shoulders are given in parentheses. Regions marked × were not examined with the lithium fluoride prism. "Form 3 trans." denotes a sample of the form 3 monohydrate which had spontaneously transformed into a yellow form at room temperature.

Bands due to the uranyl ion. The strongest band in the region 900—950 cm.$^{-1}$ in the spectra of the uranyl acetylacetones is assigned to the asymmetric stretching frequency of the uranyl ion. In other crystalline uranyl compounds this vibration has been found [9]

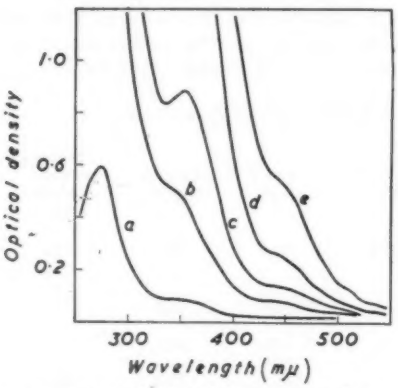
[7] Duval and Lecomte, *J. Chim. phys.*, 1953, **50**, 64.
[8] Corbridge and Lowe, *J.*, 1954, 493.
[9] Conn and Wu, *Trans. Faraday Soc.*, 1938, **34**, 1483; Lecomte and Freymann, *Bull. Soc. chim. France*, 1941, **8**, 622; Sevchenko and Stepanov, *Zhur. eksp. teor. Fiz.*, 1949, **19**, 1113 (A.E.R.E. translation No. 11/3/5/80); Jones, *J. Chem. Phys.*, 1955, **23**, 2105; Gatehouse and Comyns, unpublished work.

XUM

between 909 and 950 cm.$^{-1}$, typically near 920 cm.$^{-1}$. In forms 1 and 2 of uranyl acetylacetone monohydrate and in the anhydrous compound the frequencies are also in this range, but in form 3 of the monohydrate the frequency has the unusually low value of 905 cm.$^{-1}$. This probably reflects some abnormality in the structure of the uranyl ion in this form, which is also responsible for the abnormal colour.

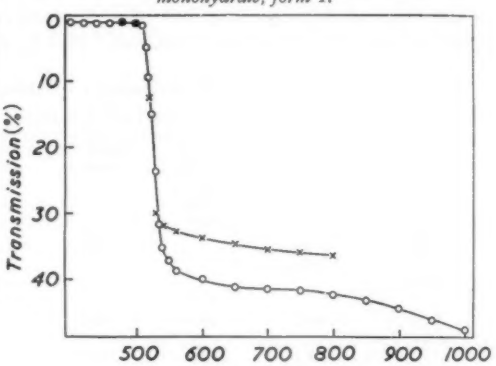
Bands due to the acetylacetone radical. Several studies have been made of the infrared spectra of acetylacetone and its metal derivatives,[10,11] and a fairly complete frequency assignment has been made by Lecomte and his co-workers.[11] Morgan [12] has reported the infrared spectrum of thorium acetylacetone, but his figure and table of frequencies are not self-consistent and both differ in many respects from the spectrum presented here.

FIG. 3. *Absorption spectra of uranyl acetylacetone solutions.*



a, *c*, *e*, in ethanol, in 10 cm. cell, 3·60 × 10^{-6}, 3·60 × 10^{-5}, and 1·80 × 10^{-4}M respectively; *b*, *d*, in benzene, in 1 cm. cell, 1·85 × 10^{-4} and 9·23 × 10^{-4}M respectively.

FIG. 4. *Absorption spectrum of uranyl acetylacetone monohydrate, form* 1.



○ At 25°. × At −196°.

When the spectra of the uranyl acetylacetones are compared with those of other metal acetylacetones between 1300 and 850 cm.$^{-1}$ (where skeletal vibrations occur) the bands in the uranyl spectra are found in the same regions but are more complex. These splittings of the skeletal bands probably result from interactions between neighbouring acetylacetone radicals.

Visible and Ultraviolet Spectra of Solutions.—Absorption spectra of solutions of anhydrous uranyl acetylacetone in ethanol and in benzene at room temperature are shown in Fig. 3. The ethanolic solutions exhibit an intense peak at 272 mμ (ε 16,400), a peak or shoulder at 353 mμ (ε 2500), a weak shoulder at 448 mμ (ε ≃ 280), and a very weak shoulder at 510 mμ (ε ≃ 60). The spectra of the benzene solutions are similar, but observations in this solvent could not be made below 300 mμ. The solutions did not fluoresce in ultraviolet light at room temperature.

The bands at 272 and 353 mμ resemble those reported for uranyl trifluoroacetylacetone

[10] Lecomte and Freymann, *Compt. rend.*, 1939, **208**, 1401; Kahovec and Kohlrausch, *Ber.*, 1940, **73**, 1304; Lecomte, *Discuss. Faraday Soc.*, 1950, **9**, 125; Bellamy, Spicer, and Strickland, *J.*, 1952, 4653; Shigorin, *Izvest. Akad. Nauk S.S.S.R., ser. Fiz.*, 1953, **17**, 596; *Idem, Zhur. fiz. Khim.*, 1953, **27**, 554; Bellamy and Branch, *J.*, 1954, 4491; Belford, Martell, and Calvin, *J. Inorg. Nuclear Chem.*, 1956, **2**, 11; Mecke and Funck, *Z. Elektrochem.*, 1956, **60**, 1124; Holtzclaw and Collman, *J. Amer. Chem. Soc.*, 1957, **79**, 3318; West and Riley, *J. Inorg. Nuclear Chem.*, 1958, **5**, 295.

[11] Duval, Freymann, and Lecomte, *Compt. rend.*, 1950, **231**, 272; *idem, Bull. Soc. chim. France*, 1952, **19**, 106.

[12] Morgan, U.S.A.E.C. report AECD–2659 (1949).

by Haszeldine and his co-workers [13] and for uranyl benzoylacetone by Sacconi and Giannoni.[2] The two weak bands, if present in the spectra of these compounds, would probably not have been observed by these workers at the concentrations they employed.

The spectra of the metal acetylacetones were studied by Sone and his co-workers [14] and by Kiss,[15] who found from 1 to 3 bands in the ultraviolet region (in Kiss's terminology, bands *d*, *e*, and *f*) due to transitions in the ligand, and bands in the visible and ultraviolet regions due to transitions in the metal ion modified by the ligand. The bands in the uranyl acetylacetone spectra at 272 and 353 mμ are clearly assignable to Kiss's bands *e* and *d* respectively. The 448 mμ band, from its position and low intensity, is almost certainly a modified form of the uranyl band. The 510 mμ band may also be due to the uranyl ion, although it falls just outside the range of bands usually observed in the spectra of uranyl ions in solution.[16]

Sacconi and Giannoni [2] assigned the bands in their spectra at 376—403 mμ to the uranyl ion, but the occurrence of these bands in the spectra of the acetylacetones of other metals, their strong intensities, and the present discovery of a band at 448 mμ, make this assignment improbable.

The solutions in benzene, as well as in other non-co-ordinating solvents including chlorobenzene and dichloroethane, become redder on heating, whereas solutions in co-ordinating solvents including ethanol, *n*-pentyl acetate, and *cyclo*hexanone do not. Anomalously, chloroform solutions do not change colour. This effect was not studied spectrophotometrically, but may result from a small broadening of the absorption bands with increasing temperature.[17]

The molecular weight of anhydrous uranyl acetylacetone in benzene at 80° corresponds with that of a dimer.

Visible Spectra of Crystals.—The visible absorption spectra of single crystals of the red (form 3) and one of the yellow (form 1) monohydrate of uranyl acetylacetone, measured at room and liquid nitrogen temperatures, are shown in Figs. 4 and 5. To examine the pleiochroism, the spectrum of the red form was obtained with polarised light.

The yellow form exhibited a sharp step at 510—540 mμ, and the red form a similar but less steep one at 550—600 mμ. At shorter wavelengths than these steps, where the uranyl absorption bands are normally found, no light was transmitted through the crystals because they were too thick. At longer wavelengths there were no absorption bands: less light was transmitted in this region at low temperatures than at high, probably owing to variation of the refractive index with temperature which would vary the ratio of transmitted to reflected light.*

The wavelength of the step in the spectrum of the yellow form corresponds with that of the resonance line observed in the absorption spectra of other crystalline uranyl compounds.[18] The step in the spectrum of the red form probably corresponds with the resonance line of a different electronic transition.

Crystals of uranyl acetylacetone monohydrate, form 1, showed a strong yellow fluorescence, and form 2 a weak yellow fluorescence, in ultraviolet light at −196° but not at +25°. Crystals of the monohydrate, form 3, and the anhydrous form, did not fluoresce. Thorium acetylacetone gave a white fluorescence at −196° but not at +25°.

Magnetic Susceptibilities.—Magnetic susceptibilities of the three monohydrates of

* We are grateful to Dr. G. T. Rogers for this suggestion.

[13] Haszeldine, Musgrave, Smith, and Turton, *J.*, 1951, 609.

[14] Sone, Miyake, Kuroya, and Yamasaki, *J. Chem. Soc. Japan*, 1948, **69**, 70; Yamasaki and Sone, *Nature*, 1950, **166**, 998; Sone, *J. Amer. Chem. Soc.*, 1953, **75**, 5207.

[15] Kiss, *Magyar Tud. Akad. Kém. Tud. Oszt. Közl.*, 1957, **9**, 257; Kiss and Császár, *Acta Chim. Acad. Sci. Hung.*, 1957, **13**, 49.

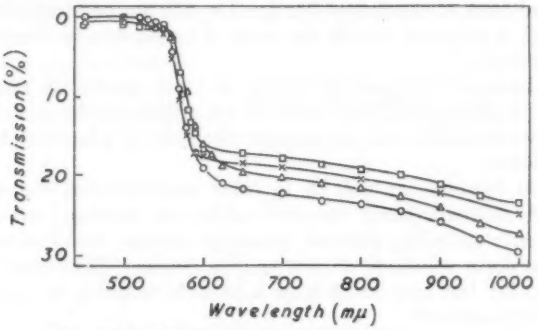
[16] Rabinowitch, " Absorption Spectra of Uranyl Compounds in Solution," U.S.A.E.C. report ANL-5173 (1953).

[17] Grubb and Kistiakowsky, *J. Amer. Chem. Soc.*, 1950, **72**, 419.

[18] Rabinowitch, " Spectroscopy of Uranyl Salts in the Solid State," U.S.A.E.C. report ANL-5122 1953).

uranyl acetylacetone and a dehydrated sample of the form 1 monohydrate were measured at 25°. A Gouy balance was used, calibrated by $CuSO_4,5H_2O$. The materials were all weakly diamagnetic, values for χ_m ranging from -52×10^{-6} to -106×10^{-6} c.g.s. units. The susceptibility calculated for $UO_2(C_5H_7O_2)_2,H_2O$ is $\chi_m = -54 \times 10^{-6}$ on assumed $\chi_m$values for the uranyl ion [19] of $+57 \times 10^{-6}$, for water [20] of -13×10^{-6}, and for the acetylacetone ion [21] of -49×10^{-6} c.g.s. units. Deviations between the individual experimental values, and between these and the calculated value, are within experimental

FIG. 5. *Absorption spectrum of uranyl acetylacetone monohydrate, form* 3.



○: +25°, electric vector parallel to *c*-axis
×: −196° ,, ,, ,,
△: +25°, electric vector at right angles to *c*-axis
□: −196°, ,, ,, ,,

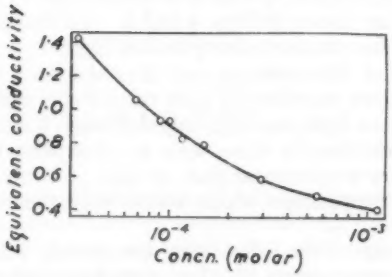


FIG. 6. *Equivalent conductivity of uranyl acetylacetone at* 0·2°.

error. There is thus no major difference between the magnetic properties of the uranyl ions in these compounds.

Electrical Conductivities.—When uranyl acetylacetone monohydrate was added to conductivity water at 25° the conductivity rose as the crystals dissolved, and then fell rapidly. After about 20 min. the solution was opalescent and in a few hours a precipitate of $UO_3,2H_2O$ formed.

When the experiment was performed at 0·2° the conductivity rose as the crystals dissolved, and when they had all dissolved it continued to rise but much more slowly. This second rise was linear for several hours, and extrapolation to the time of addition of the crystals gave an approximate value for the equivalent conductivity of the solution before the onset of the process responsible for the second rise. The variation with concentration of the extrapolated conductivity at 0·2° is shown in Fig. 6. Extrapolation of the curves obtained at 25° was impossible, but the conductivities at the maxima of the curves

[19] Freed and Kasper, *J. Amer. Chem. Soc.*, 1930, **52**, 4671; Lawrence, *ibid.*, 1934, **56**, 776.
[20] Selwood, "Magnetochemistry," Interscience, New York, 1956, p. 85.
[21] Hutchison and Elliott, *J. Chem. Phys.*, 1948, **16**, 920.

at concentrations between 4×10^{-5} and 2×10^{-4}M were about three times as great as the extrapolated conductivities at corresponding concentrations at 0·2°.

From the work of Rydberg [22] and of Fernelius and his co-workers [23] it is reasonable to assume that the following two equilibria are responsible for the extrapolated conductivities at 0·2°:

$$UO_2Acac_2 \rightleftharpoons UO_2Acac^+ + Acac^-$$
$$UO_2Acac^+ \rightleftharpoons UO_2^{++} + Acac^-.$$

The cause of the slow rise in conductivity at 0·2° is obscure.

At 25° the net reaction is

$$UO_2Acac_2 + 3H_2O = UO_3,2H_2O + 2H\,Acac$$

Probably the two reactions postulated at 0·2° occur immediately on dissolving the crystals in water, and these are followed by a succession of hydrolytic steps which reduce the conductivity essentially to that of aqueous acetylacetone. The uranyl ion is known to be extensively hydrolysed [24] in solutions of pH > 3, and although the pH values of the very dilute solutions of the complexes were not measured they must have exceeded this.

Reactions.—In common with other uranyl diketone complexes,[2] uranyl acetylacetone forms an addition compound with pyridine,[25] and double salts of the type $R^+[UO_2(C_5H_7O_2)_3]^-$ (where $R^+ = NH_4^+$, $CH_3{\cdot}NH_3^+$, $C_6H_5{\cdot}NH_3^+$) have also been described.[25]

When uranyl acetylacetone is crystallised from co-ordinating organic solvents, the product is usually solvated. Solvates with ethanol, dioxan, acetylacetone, and acetophenone have now been prepared, all of which contain one molecule of solvent to each uranium atom.

When an attempt was made to prepare a uranyl acetylacetone perchlorate analogous with the compound $Mn(C_5H_7O_2)_2,ClO_4(H_2O)_2$ described by Cartledge,[26] by triturating uranyl acetylacetone monohydrate with perchloric acid, the product was identical with the solvate obtained by crystallising uranyl acetylacetone from acetylacetone. Evidently some of the uranyl complex is decomposed with liberation of free acetylacetone, which then combines with the remainder of the complex.

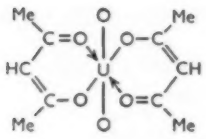
The monohydrates of uranyl acetylacetone are readily dehydrated at 100° under vacuum, the crystals falling to an orange powder. The anhydrous forms yielded by the three monohydrates gave almost identical infrared spectra. Contrary to Abrahamson and Brown's observations,[5] the anhydrous material took up water only very slowly on exposure to the atmosphere. The anhydrous material can be crystallised from dichloroethane [6] or from chlorobenzene: in both cases precautions must be taken to exclude moisture, or the monohydrate (form I) is produced.

Discussion

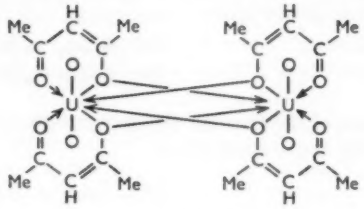
That uranyl acetylacetone cannot be represented by the simple formula (I) is shown by the ebullioscopic measurements. The dimeric molecules in benzene may be held together in one of several ways: by acetylacetone bridges, by co-ordination of the uranyl oxygen atoms to the adjacent uranium atoms, or by co-ordination of the acetylacetone oxygen atoms to the adjacent uranium atoms. The third possibility seems the most likely; if only one oxygen atom from each molecule were co-ordinated in this way then

[22] Rydberg, *Arkiv Kemi*, 1955, **8**, 113; *idem*, *Svensk kem. Tidskr.*, 1955, **67**, 499.
[23] Izatt, Fernelius, and Block, *J. Phys. Chem.*, 1955, **59**, 80; and other papers in this series.
[24] Sutton, *J.*, 1949, S275; Ahrland, *Acta Chem. Scand.*, 1949, **3**, 374; Ahrland, Hietanen, and Sillén, *ibid.*, 1954, **8**, 1907; Hearne and White, *J.*, 1957, 2168.
[25] Hager, *Z. anorg. Chem.*, 1927, **162**, 82.
[26] Cartledge, *J. Amer. Chem. Soc.*, 1952, **74**, 6015.

the uranium atoms would have a co-ordination number of seven, and if two were co-ordinated the co-ordination number would be eight. The latter possibility is shown diagrammatically in (II), no assumptions being made about the nature of the bonds.



(I)



(II)

The molecular complexity in co-ordinating solvents may well be less than in benzene, since co-ordination by solvent molecules is probably easier sterically than co-ordination of type (II): both processes could, however, occur together. The involatility of anhydrous uranyl acetylacetone [4, 6] suggests that the molecules are polymerised in the crystal as well as in benzene solution.

The cause of the unusual colour of the monohydrate, form 3, is obscure; perhaps the configuration of the atoms surrounding the uranyl ions, or the co-ordination number of the uranium atoms, is unusual. The uranyl ions must have substantially the same structure in all the monohydrates since, if the ions were bent, the symmetric stretching frequency would appear in the infrared spectrum, and if any other atoms were attached through the uranyl oxygen atoms then the asymmetric stretching frequency would be markedly shifted. The small decrease in the asymmetric stretching frequency observed in the red monohydrate may be due to a small lengthening of the U–O bonds.

Experimental

Acetylacetone (B.D.H.) was dried (K_2CO_3) and fractionated in a Widmer column, b. p. 132—134°. Dichloroethane (Tyrer) was shaken with water to remove acid, and dried (Na_2SO_4).

Analyses for uranium were made by ignition to 750—850° for several hours and weighing the residual U_3O_8. Some commercial carbon and hydrogen analyses were made, but the results were unreliable.

Probably all the hydrates, other than that made by crystallisation from dichloroethane, were slightly contaminated by $UO_3,2H_2O$. Crystals of all three forms, when dissolved in alcohol or dichloroethane on a microscope slide, left faint ' ghosts ' of minute insoluble particles. This contamination was probably responsible for the small variation in uranium content observed between different batches of the same form.

Preparations.—Form 1. This was the most commonly obtained form. Sodium hydroxide solution (3·0N) was added dropwise to a solution of uranyl nitrate hexahydrate (10·0 g.) and acetylacetone (4·0 ml.) in water (30 ml.) at 80°. Crystallisation started when 9 ml. of alkali had been added, and the mixture was then allowed to cool slowly to room temperature. The crystals (form 1) were filtered off, yield 6·8 g. [Found: U, 48·87, 48·88, 48·99. Calc. for $UO_2(C_5H_7O_2)_2,H_2O$: U, 48·97%].

Crystals of form 1 (10 g.) from a similar, larger preparation were crystallised from dichloroethane (60 ml.), the hot solution being first decanted from a small amount of yellow solid. The crystals, also of form 1, were filtered off, yield 8·2 g. (Found: U, 48·88, 48·85, 48·85, 48·84%). A portion was dehydrated over P_2O_5 for 5 hours at 100°/0·02 mm. and gave a fine orange powder [Found: U, 50·69, 50·70, 50·59, 50·67. Calc. for $UO_2(C_5H_7O_2)_2$: U, 50·85%].

Form 2. When almost any preparation was filtered before crystallisation was complete, the crystals deposited by the filtrate were of form 2. Crystals so obtained were ground between glass slides, and the powder was used to seed a preparation similar to one which usually gave form 1 in the absence of seeding.

Sodium hydroxide solution (16 ml., 3·0N) was added slowly to a solution of uranyl nitrate hexahydrate (20·0 g.) and acetylacetone (8 ml.) in water (200 ml.) at 75°. The solution was

seeded and allowed to cool slowly. The crystals (form 2) were filtered off, yield 6·5 g. (Found: U, 49·19, 49·29, 49·22%). A portion was dehydrated (over P_2O_5) for 6 hr. at 100°/0·02 mm. and gave a fine orange powder (Found: U, 51·13, 50·62, 50·63%).

Form 3. It was difficult to obtain crystals of this form at will, and preparations were often contaminated by crystals of form 1 or 2. This form was usually produced under conditions of high supersaturation.

The preparation which first yielded crystals of form 3 was made as follows. Acetylacetone (0·36 ml., B.D.H., not further purified) was added to aqueous uranyl nitrate (5 ml., containing 0·89 g. of the hexahydrate) and the mixture heated nearly to the b. p. Sodium hydroxide solution (0·9 ml., 3·21N) was added dropwise, the last few drops giving a slight precipitate (probably of $UO_3,2H_2O$). The solution was allowed to cool: when the temperature reached 47° crystallisation occurred very rapidly, giving small red needles, yield 0·39 g. (Found: U, 49·2, 48·6%).

It was prepared on a larger scale by adding sodium hydroxide solution (16 ml., 3·0N) to uranyl nitrate hexahydrate (20·0 g.) and acetylacetone (8 ml. of the purified product) in water (60 ml.) at 65°, and seeding with crystals from the first preparation. The product (form 3, contaminated by a very few crystals of form 1) was filtered off and dried in air, yield 8·1 g. (Found: U, 48·25, 48·26, 48·32, 48·28%). After drying over KOH for 1½ hours at 20°/10 mm. the analysis was substantially unchanged (Found: U, 48·31, 48·11, 48·30). A portion was dehydrated (P_2O_5) for 3½ hr. at 100°/0·02 mm. and gave a fine orange powder resembling that from forms 1 and 2 (Found: U, 50·99, 50·89, 50·99%).

Thorium acetylacetone was prepared by mixing aqueous solutions of thorium nitrate and sodium acetylacetone, and extracting the precipitate with hot toluene. The toluene solution crystallised on standing and the product was recrystallised from warm toluene, m. p. 170·5° (Marchi [27] reported m. p. 171°).

Crystallography.—Densities were determined by flotation in mixtures of tetrabromoethane and tetralin, pre-saturated with uranyl acetylacetone.

Copper K_α radiation ($\lambda = 1{\cdot}542$ Å) was used. The following diffraction photographs were obtained:

Form 1*A*. Oscillation photographs, and zero to third layer equi-inclination Weissenberg photographs about the *b* axis.

Form 1*B*. Oscillation photographs about the *a*, *b*, and *c** axes; equi-inclination Weissenberg photographs of the zero to fourth layers about the *a* axis, and of the zero to third layers about the *b* axis.

Form 2. Oscillation photographs, and zero to second layer equi-inclination Weissenberg photographs about both *a* and *b* axes.

Form 3. Oscillation photographs, and zero to second layer equi-inclination Weissenberg photographs about the *c* axis.

X-Ray powder photographs of forms 1 and 2, and of the transformation products of forms 1 and 3, were taken with a Guinier-type focusing camera.

Infrared Spectra.—Samples were examined as Nujol mulls between sodium chloride plates. The spectra from 700 to 3000 cm.$^{-1}$ were obtained in a Grubb-Parsons double-beam infrared spectrophotometer with an S3A monochromator and a sodium chloride prism. The spectra from 3000 to 3800 cm.$^{-1}$ were obtained on a Hilger double-beam infrared spectrophotometer, model H 800, with a lithium fluoride prism.

Visible and Ultraviolet Absorption Spectra.—The Harwell recording spectrophotometer was used to obtain the solution spectra. The crystal spectra were measured by Dr. G. T. Rogers on a Unicam spectrophotometer, model SP.500, in conjunction with a cell previously described.[28] The crystal of form 1 was 0·21 mm. thick, with approximately parallel faces, and completely covered the hole (1 mm. diam.) in the metal block on which it was mounted. No single crystal of form 3 was available which would completely cover this hole, so seven long crystals, ranging in thickness from 0·15 to 0·20 mm., were laid side by side over the hole and glued in position.

Conductance Measurements.—Measurements were made at 1000 c.p.s. with a bridge similar to that described by Luder.[29] Tests, in which the cell was replaced by a standard resistance box in parallel with a variable air capacitor, showed that the bridge was accurate to ±0·2%.

[27] Marchi, Ph.D. Thesis, Ohio, 1942, p. 40.
[28] Mclaren and Rogers, *Proc. Roy. Soc.*, 1957, *A*, **240**, 484.
[29] Luder, *J. Amer. Chem. Soc.*, 1940, **62**, 89.

The cell was made of "Pyrex" glass in the form of a cylinder 9 cm. high by 4 cm. diam., with a restricted opening at the top and the electrodes set vertically in the base. The electrodes were of bright platinum, about 2·5 cm. square and 3 mm. apart. A tube which joined the base of the cell served to admit a stream of argon to expel carbon dioxide. The cell-constant was measured by comparison with a cell of larger cell-constant, which had been calibrated by 0·01D-potassium chloride solution; the value at 25° was 0·0358 cm.$^{-1}$ and its variation with temperature was neglected.

The 25° thermostat was a stirred bath of "liquid paraffin," regulated to better than $\pm$0·05° by a variable-contact mercury thermometer. The thermostat used for the low-temperature work was a metal can of stirred kerosene standing in a stirred bath of ice and water: the temperature of the kerosene remained at 0·2 $\pm$ 0·1° for several hours after filling the ice-bath.

The water was purified by distilling "AnalaR" redistilled water, slightly acidified by potassium hydrogen sulphate, in a simple "Pyrex" still, and collecting it in a silica flask. Soon after preparation, and after removal of carbon dioxide, it had a specific conductance of about $1{\cdot}2 \times 10^{-7}$ ohm^{-1} at 25°, or 3×10^{-8} ohm^{-1} at 0·2°.

Procedure. A standard quantity (44·6 g.) of water was weighed into the cell and a rapid stream of argon, pre-saturated with water at the same temperature as the cell, was bubbled through it. The stream was interrupted momentarily as each measurement was made. After about 30 min. the conductivity remained constant: on prolonged bubbling of argon the conductivity slowly rose, presumably owing to the solution of ions from the glass or impurities from the argon. When the conductivity had become constant a weighed quantity of uranyl acetylacetone hydrate (form 1, finely ground) was added and measurements were made every minute.

For the experiments at 0·2° the cell was transferred to the cold thermostat after most of the carbon dioxide had been removed from the water, and argon was bubbled again until the conductivity was constant.

In the experiments at 25° the conductivity maxima were observed as the last particles of solid were dissolving. In the experiments at 0·2° the change of slope of the curve occurred also at about this time, but solution was much slower at 0·2° than at 25°.

Identification of the hydrolysis product. Saturated aqueous uranyl acetylacetone was allowed to stand for 2 days in air at room temperature. The fine yellow precipitate was washed once by decantation and then filtered off and allowed to dry in the air. *X*-Ray powder photographs, taken with a Guinier-type focusing camera, were identical with those of $UO_3,2H_2O$ samples.[30]

Solvates.—Crystallisation of uranyl acetylacetone from ethanol. Uranyl acetylacetone monohydrate, form 1 (2·66 g.), was dissolved in warm ethanol (2 ml.) and the solution filtered. The filtrate deposited crystals of the *uranyl acetylacetone–ethanol* adduct at room temperature, and the yield was improved (to 1·48 g.) by cooling to 0° [Found: U, 46·0, 45·9. $UO_2(C_5H_7O_2)_2,C_2H_5{\cdot}OH$ requires U, 46·3%].

Crystallisation of uranyl acetylacetonate from acetylacetone. Uranyl acetylacetone monohydrate, form 1 (5·0 g.), was crystallised from warm acetylacetone (15 ml.). The resulting *uranyl acetylacetone–acetylacetone* adduct (4·8 g.) consisted of small, orange, 6-sided, twinned plates [Found: U, 41·7, 41·6, 41·6. $UO_2(C_5H_7O_2)_2,C_5H_8O_2$ requires U, 41·9%].

Reaction of uranyl acetylacetone with perchloric acid. Aqueous perchloric acid (1·87N) was added dropwise to uranyl acetylacetone monohydrate, form 1 (5·0 g.), and the mixture stirred continuously. When 5 ml. of acid had been added some of the crystals had dissolved, but the remainder were almost unchanged. Addition of a further 0·6 ml. of acid caused these crystals to dissolve rapidly, crystals of a new compound being simultaneously deposited. These new crystals were filtered off and dried (NaOH), yield 2·5 g. Their microscopical appearance was identical with that of the uranyl acetylacetone–acetylacetone adduct (Found: U, 41·7, 41·2%).

Crystallisation of uranyl acetylacetone from acetophenone. Uranyl acetylacetone monohydrate, form 1 (5·0 g.), was dissolved in warm acetophenone (20 ml.). Slow cooling produced large orange crystals (4·0 g.) of the *uranyl acetylacetone–acetophenone* adduct [Found: U, 40·3, 40·2. $UO_2(C_5H_7O_2)_2,C_8H_8O$ requires U, 40·5%].

Crystallisation of uranyl acetylacetone from dioxan. Uranyl acetylacetone monohydrate, form 1 (4·0 g.), was dissolved in boiling dioxan (20 ml.) and the hot solution filtered from a small amount of yellow solid (probably a UO_3 hydrate). The *uranyl acetylacetone–dioxan* adduct

[30] Dawson, Wait, Alcock, and Chilton, *J.*, 1956, 3531.

(1·5 g.) crystallised on cooling [Found: U, 42·4, 42·2, 42·4, 42·2. $UO_2(C_5H_7O_2)_2,C_4H_8O_2$ requires U, 42·8%].

Ebullioscopic Measurements.—These were made by Dr. D. C. Bradley, using his technique.[31] Over the concentration range 0·0216—0·3541 g. of uranyl acetylacetone to 15·95 g. of benzene the b. p. rose linearly, with a slope of 0·200° per g. {Found: *M*, 913. Calc. for $[UO_2(C_5H_7O_2)_2]_2$: *M*, 937}.

We are grateful to Professor R. S. Nyholm, F.R.S., and Dr. A. G. White for valuable discussions, to Mr. J. V. F. Best for the ultraviolet solution spectra, to Dr. D. C. Bradley for the ebullioscopic measurements, to Dr. J. Gaunt and Mr. A. M. Deane for the infrared spectra, and to Dr. G. T. Rogers for the visible spectra of the crystals, and to Mrs. G. W. Stuart for the *X*-ray powder photographs.

Chemistry Division, Atomic Energy Research Establishment,
Harwell, Berks.
Sir William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1. [*Received, November 1st*, 1957.]

[31] Bradley, Gaze, and Wardlaw, *J.*, 1955, 3977.

---

939. *Interdependence of Conformation and Conjugation in Aromatic Ethers. Part III.*[1]

By G. Baddeley and M. A. Vickars.

The ultraviolet absorption spectra and rates of bromination of coumaran and its 2-methyl and 2 : 2-dimethyl derivatives and the rates of solvolysis of their chloromethyl derivatives in 90% aqueous ethanol have been determined and compared with the corresponding data for the ethers PhOR, where R is Et, Pr^i, and Bu^t. The comparison shows that, in the absence of steric interaction of the *tert.*-butyl group and the benzene ring, *tert.*-butoxybenzene and its chloromethyl derivative would react about three times faster than they do.

Reactivity decreases in the order 2-methyl- > 2 : 2-dimethyl-coumaran > coumaran.

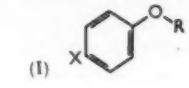
In Part I [1] and earlier communications [2] the effects of alkyl groups R and of the value of *n* on the ultraviolet absorption spectra and rates of bromination of the ethers (I) and (II) respectively (X = H) and on the rates of solvolysis of their chloromethyl derivatives (X = CH_2Cl) have been offered as evidence for a relation between conformation and conjugation of an ether-oxygen atom and a benzene ring. The extinction coefficients of *tert.*-butoxybenzene and homochroman (II; $n = 3$), the rates of bromination of these ethers, and the rates of solvolysis of their chloromethyl derivatives are all comparatively small, and these anomalies have been explained in terms of increase of steric interaction with decrease of the interplanar angle of the ether group and the benzene ring in these compounds. In the ethers (I; X = H) and their chloromethyl derivatives reactivity increases in the order R = Bu^t < Me < Et < Pr^i which is compatible with the view that these alkyl groups have an inductive effect which increases in the order Me < Et < Pr^i < Bu^t, and that that of the *tert.*-butyl group is more than counterbalanced by steric interaction of this group and the benzene ring. This view requires that, should steric interaction be circumvented, R would affect the reactivity of these compounds only by induction; the work described in this paper was designed to achieve this simplification and thereby to measure the effect of steric interaction on the reactivity of *tert.*-butoxybenzene and its chloromethyl derivative.

The carbon atoms of the heterocyclic ring of coumaran (II; $n = 1$; X = H) are held

[1] Part I, Baddeley, Smith, and Vickars, *J.*, 1956, 2455; Part II, Baddeley and Cooke, *J.*, 1958, 2797.

[2] Baddeley and Smith, *Nature*, 1949, **164**, 1014; Baddeley, Holt, Smith, and Whittaker, *ibid.*, 1951, **168**, 386.

in, or close to, the plane of the benzene ring and conjugation of the oxygen atom and the benzene ring should not be altered by steric interaction when the hydrogen atoms of the



(I) (II)

2-methylene group are replaced by bulky groups. Evidence for this view is provided by the ultraviolet absorption spectra of coumaran and its 2-methyl and 2 : 2-dimethyl derivatives; they are nearly identical. The compounds have three absorption peaks in the region 2500—2900 Å (see p. 4668); wavelengths and extinction coefficients for the middle peaks are listed in Table 1, together with those for the corresponding peaks of some related

TABLE 1. *Comparison of the ultraviolet absorption spettra of the ethers.*

	C_6H_4·O·CRR′·CH_2		C_6H_5·O·CRR′·CH_3	
	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε
R = R′ = H	2830	3095	2710	1938
R = Me, R′ = H	2820	3090	2730	1920
R = R′ = Me	2820	3070	2700	454
	Ethyl *o*-tolyl ether		2720	1744

alkyl phenyl ethers. Having thus demonstrated that steric hindrance of conjugation does not occur in 2-methyl- and 2 : 2-dimethyl-coumaran, it is reasonable to assume that such hindrance cannot affect the rates of bromination of these ethers and of solvolysis of their chloromethyl derivatives.

The Arrhenius parameters for solvolysis of the chloromethyl derivatives in 90% aqueous ethanol are listed in Table 2, and in Table 3 the reactivities of these chlorides are compared with those of the chloromethyl derivatives of the corresponding alkyl aryl ethers. The corresponding comparison for the bromination of the ethers in acetic acid is provided by Table 4; the time intervals for 20% consumption of bromine and therefrom the calculated relative rates of bromination are listed. As was expected, there is an overall resemblance between the two comparisons. They show that in the absence of steric interaction of the

TABLE 2. *Arrhenius parameters for the solvolysis of the chlorides in* 90% *aqueous ethanol.*

CH_2Cl·C_6H_3·O·CRR′·CH_2	$10^3k_{0°}$ (min.$^{-1}$)	$10^3k_{10°}$ (min.$^{-1}$)	$10^3k_{15°}$ (min.$^{-1}$)	$10^3k_{25°}$ (min.$^{-1}$)	E (kcal./mole)	$10^{-11}A$ (min.$^{-1}$)
R = R′ = H	25·4	77·8	132	—	17·3	15
R = Me, R′ = H	47·9	146	248	—	17·2	24
R = R′ = Me	36·0	109	184	—	17·1	15
4 : 3-MeO·C_6H_3Me·CH_2Cl	2·50	8·91	16·3	51·1	19·7	107
4 : 3-EtO·C_6H_3Me·CH_2Cl	4·76	16·6	29·9	91·9	19·3	110

TABLE 3. *Comparison of energies of activation and rates of solvolysis of the chlorides.*

	CH_2Cl·C_6H_3·O·CRR′·CH_2 in 90% aq. EtOH			CH_2Cl·C_6H_4·O·CRR′·CH_3 in 90% aq. EtOH			C_6H_4·CHCl·CRR′·CH_3 in EtOH (ref. 3)	
	$10^3k_{0°}$ (min.$^{-1}$)	$k_{rel.}$	E (kcal./mole)	$10^3k_{25°}$ (min.$^{-1}$)	$k_{rel.}$	E (kcal./mole)	$k_{rel.}$	E (kcal./mole)
R = R′ = H	25·4	100	17·3	18·5	100	20·3	100	21·6
R = Me, R′ = H	47·9	189	17·2	32·5	176	18·8	12	22·8
R = R′ = Me	36·0	142	17·1	8·20	44	20·8	2	23·0

tert.-butyl group and the benzene ring the rates of reaction of *tert.*-butoxybenzene and of its chloromethyl derivative would both be about three times faster than they are. It is noteworthy that the coefficients of ultraviolet absorption by this ether are about a quarter of what they would be in the absence of steric hindrance of conjugation (see Table 1).

The comparisons provided by Tables 1, 3, and 4 confirm our previous conclusion that doubtless as a consequence of the imposed coplanarity of the ether group and the benzene

TABLE 4. *Comparison of the rates of interaction of the ethers* (M/200) *and bromine* (M/1000) *in acetic acid at* 20°.

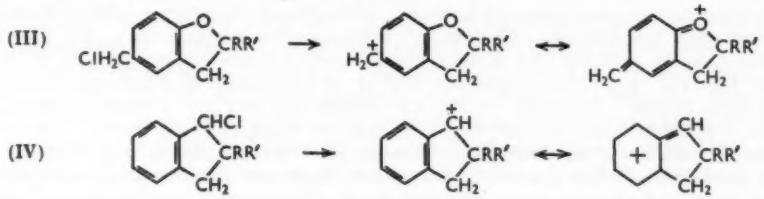
	C_6H_4·O·CRR′·CH_2		C_6H_5·O·CRR′·CH_3		*o*-C_6H_4Me·O·CRR′·CH_3
	$t_{20\%}$ (sec.)	$k_{rel.}$	$t_{20\%}$ (sec.)	$k_{rel.}$	$t_{20\%}$ (sec.)
R = R′ = H	15·5	100	342 *	100	78
R = Me, R′ = H	9·0	170	270	127	—
R = R′ = Me	11·5	140	786	44	—
			o-C_6H_4Me·OMe		186

* In Part I, $t_{20\%}$ for PhOEt (M 100) was wrongly given as 1·44 min.; the correct value is 2·80 min.

ring, the five-membered heterocyclic ring of coumaran and its derivatives enhances conjugation.

As to the effect of 2-methyl substituents on the rate of reaction of coumaran and its chloromethyl derivative, the data show that whereas one methyl group, doubtless by its inductive effect, increases the rate, the increase is nearly halved by the second methyl group. This anomaly indicates that together the two methyl groups may hinder solvation, which is especially important in the polar transition states of bromination and solvolysis, or provide a positively charged envelope of hydrogen atoms which opposes those electronic displacements which give the neighbouring oxygen atom a positive charge. These possibilities must also be borne in mind when interpreting the behaviour of *tert.*-butoxybenzene and its chloromethyl derivative.

In conclusion we wish to indicate that the ionisation processes (III) and (IV) are sufficiently closely related to make it likely that the factors which make the rate of the former decrease in the order R = Me, R′ = H > R = R′ = Me will contribute to the corresponding decrease in the latter [3] (see Table 3).



EXPERIMENTAL

Materials.—Ethers. Coumaran,[1] b. p. 78—81°/15 mm., n_D^{20} 1·5524 (picrate, m. p. 75—76°), 2-methylcoumaran,[4] b. p. 80°/17 mm., n_D^{17} 1·531 (Found: C, 80·9; H, 7·4. Calc. for $C_9H_{10}O$: C, 80·6; H, 7·5%), 2 : 2-dimethylcoumaran,[5] b. p. 76—77°/15 mm., n_D^{20} 1·517 (Found: C, 81·0; H, H, 7·9. Calc. for $C_{10}H_{12}O$: C, 81·1; H, 8·1%), and ethyl *o*-tolyl ether,[6] b. p. 181—182°, n_D^{20} 1·5051, were prepared as described in the literature cited.

Hydroxymethyl Derivatives from the Ethers.—5-Hydroxymethylcoumaran. A solution of acetyl chloride (2 mol.) and aluminium chloride (1 mol.) in ethylene dichloride at −10° was added with stirring to a cooled solution of coumaran in diethylene chloride. The temperature of the mixture was not allowed to exceed −6° and after 5 min. the mixture was poured on ice and hydrochloric acid. The organic layer was separated and, together with the ethylene dichloride extracts of the aqueous layer, was washed successively with water, dilute alkali, and water, and dried (K_2CO_3). Removal of the solvent gave *5-acetylcoumaran*, which separated from light petroleum in needles, m. p. 61—63° (Found: C, 74·1; H, 6·1. $C_{10}H_{10}O_2$ requires C, 74·1; H, 6·2%). Hypochlorite oxidation [7] of the ketone gave *coumaran-5-carboxylic acid* which separated from ethanol in slender needles, m. p. 188—190° (Found: C, 65·8; H, 4·9%; equiv., 162.

[3] Baddeley, Rasburn, and Rose, *J.*, 1958, 3168.
[4] von Auwers, *Annalen*, 1918, **415**, 150; Adams and Rindfusz, *J. Amer. Chem. Soc.*, 1919, **41**, 656.
[5] Adams, Bartz, and Miller, *ibid.*, 1935, **57**, 371.
[6] Staedel, *Annalen*, 1883, **217**, 41.
[7] Newman and Holmes, *Org. Synth.*, Coll. Vol. II, 1943, p. 428.

$C_9H_8O_3$ requires C, 65·9; H, 4·9%; equiv., 164). Reduction of the ethyl ester by lithium aluminium hydride gave the required alcohol,[1] b. p. 158—160°/11 mm., n_D^{18} 1·5776 (phenylurethane,[1] m. p. 88—89°).

5-Hydroxymethyl-2-methylcoumaran. The experimental procedure was similar to that in the preparation of 5-hydroxymethylcoumaran. 5-Acetyl-2-methylcoumaran,[8] b. p. 163—164°/20 mm. (oxime,[8] m. p. 84—85°), melted at 8—9°, and gave *2-methylcoumaran-5-carboxylic acid* which separated from ligroin in short needles, m. p. 149—150° (Found: C, 67·6; H, 5·5%; equiv., 174. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·6%; equiv., 178). The required *alcohol*, b. p. 155—158°/14 mm. (Found: C, 73·0; H, 7·3. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%), gave a *phenylurethane* which separated from light petroleum in short needles, m. p. 106—107° (Found: C, 72·5; H, 6·1; N, 4·8. $C_{17}H_{17}O_3N$ requires C, 72·1; H, 6·0; N, 5·0%).

5-Hydroxymethyl-2 : 2-dimethylcoumaran. *5-Acetyl-2 : 2-dimethylcoumaran* separated from light petroleum in highly refractive prisms, m. p. 84—85° (Found: C, 75·5; H, 7·4. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·5%). *2 : 2-Dimethylcoumaran-5-carboxylic acid* separated from aqueous ethanol in flat needles, m. p. 174—176° (Found: C, 69·0; H, 6·3%; equiv., 191. $C_{11}H_{12}O_3$ requires C, 68·8; H, 6·2%; equiv., 192). The required *alcohol*, b. p. 158—160°/14 mm., n_D^{18} 1·5575 (Found: C, 73·9; H, 8·0. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%), gave a *phenylurethane* which separated from light petroleum in needles, m. p. 69—70° (Found: C, 72·4; H, 6·2; N, 4·9. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4; N, 4·7%).

4-Ethoxy-3-methylbenzyl alcohol, b. p. 141—143°/10 mm., m. p. 81—82° (Found: C, 72·5; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%) [*phenylurethane*, m. p. 85—86° (Found: C, 71·7; H, 6·6; N, 5·0. $C_{17}H_{19}O_3N$ requires C, 71·6; H, 6·7; N, 4·9%)], was afforded by reduction of 4-ethoxy-3-methylbenzaldehyde,[9] m. p. 31—32°.

Chloromethyl Derivatives from the Ethers.—These were prepared from the hydroxymethyl compounds: Solutions of these alcohols (*ca.* 3 g.) in light petroleum (b. p. 60—80°; 500 c.c.) at 0° were saturated with dry hydrogen chloride; the solutions were dried ($CaCl_2$), solvent was volatilised at 40° under reduced pressure, and the residues were extracted with light petroleum (b. p. <40°). Removal of solvent afforded the required chloromethyl derivatives which were flash-distilled in nitrogen at reduced pressure. This general procedure minimised formation of resins and gave the following chlorides: 5-chloromethylcoumaran,[1] m. p. 41—42° (Found: Cl, 20·5. Calc. for C_9H_9OCl: Cl, 21·0%); *5-chloromethyl-2-methylcoumaran*, b. p. 95°/0·7 mm. (Found: Cl, 19·0. $C_{10}H_{11}OCl$ requires Cl, 19·4%); *5-chloromethyl-2 : 2-dimethylcoumaran*, b. p. 93°/0·7 mm. (Found: Cl, 17·9. $C_{11}H_{13}OCl$ requires Cl, 18·1%); 4-ethoxy-3-methylbenzyl chloride, b. p. 87°/0·2 mm. (Found: Cl, 18·8. Calc. for $C_{10}H_{13}OCl$: Cl, 19·0%).

Rates of Solvolysis of the Chloromethyl Derivatives.—The solvent was 90% aqueous ethanol and the procedure was that previously described.[1] Each rate determination was repeated two or three times and at more than one temperature. The average rate coefficients and other Arrhenius parameters are listed in Table 2. The rate constants are accurate to ±1·5%, and the values of E to ±0·3 kcal./mole.

Rates of Bromination of the Ethers in Acetic Acid.—These rates were measured by the technique used by Robertson, de la Mare, and Johnston;[10] the times for 20% reaction with the ether (0·005M) and bromine (0·001M) in acetic acid at 20·0° and the relative rates are listed in Table 4.

Ultraviolet Absorption Spectra of the Ethers in Hexane.—These were measured by means of a Hilger "Uvispek" photoelectric spectrophotometer. The solvent was purified in the manner previously described.[1] The values of $\lambda_{max.}$ and ε are listed in Table 5.

TABLE 5. *Ultraviolet absorption spectra of the ethers in hexane.*

	$\lambda_{max.}$			ε		
Coumaran	2890	2830	2740 *	3055	3095	2250
2-Methylcoumaran	2890	2820	2750 *	2790	3090	2460
2 : 2-Dimethylcoumaran	2890	2820	2740 *	2770	3070	2335
Ethyl *o*-tolyl ether	2780	2720	2600 *	1666	1744	800

* Shoulder.

MANCHESTER COLLEGE OF SCIENCE AND TECHNOLOGY,
MANCHESTER, 1.

[*Received, April* 23*rd*, 1958.]

[8] Arnold and McCool, *J. Amer. Chem. Soc.*, 1942, **64**, 1316.
[9] Gattermann, *Annalen*, 1907, **357**, 355.
[10] Robertson, de la Mare, and Johnston, *J.*, 1943, 276.

XUM

940. *The Chemical Effects of γ-Radiation on Organic Systems. Part I. The Systems Pyridine–Bromobenzene and Aniline–Bromobenzene.*

By G. A. Swan and P. S. Timmons.

γ-Irradiation of a mixture of pyridine and bromobenzene afforded 2-, 3-, and 4-phenylpyridine, as well as pyridine hydrobromide. From an irradiated mixture of aniline and bromobenzene, 2- and 4-aminodiphenyl, azophenine, and aniline hydrobromide were isolated. These reactions are apparently initiated by homolysis of bromobenzene under the influence of γ-rays.

Although a number of studies of the radiation chemistry of pure organic compounds (as opposed to dilute, aqueous solutions of such compounds) have been carried out, the irradiation products have been isolated and satisfactorily characterised in only a very few cases.[1] In this and subsequent papers we describe some results of work initiated in these laboratories when, about four years ago, a ^{60}Co source of γ-radiation (nominally 100 c) was installed. In a wider fundamental study of the products of γ-irradiation of pure organic compounds and mixtures thereof, one line of work was concerned with mixtures of bromobenzene and various amines. We chose bromobenzene because of the relative inertness of its halogen atom towards most chemical reagents: if radiation activated the halogen, useful reactions might be possible.

It is well known that, particularly in aqueous solutions, oxygen often affects the course of a radiochemical reaction. Although we hope to investigate the effect of oxygen and of temperature on certain of our systems, our irradiations, except when otherwise stated, have hitherto been performed at room temperature in glass vessels stoppered in the normal way, without precautions to exclude air. The bulk of the starting materials were usually recovered unchanged; yields are expressed as G values (the number of molecules of product corresponding to an energy absorption of 100 ev). Where the yield is based only on the weight of product isolated, the G value should be regarded only as a minimum value.

When mixtures of various amines with bromobenzene were irradiated, the crystalline amine hydrobromide generally separated in amount showing linear dependence on the total dose of radiation up to the maximum studied (about 7×10^{20} ev/ml.) (in certain cases the hydrobromide separated only when the mixture was diluted with ether, after irradiation). Thus hydrogen bromide was produced during the irradiation: the rate of its production increased according to the following order of amines: dimethylaniline, diethylaniline, pyridine, ethylaniline, dibenzylamine, benzylamine, aniline, trimethylamine, ethylamine, diethylamine, triethylamine. Very little is known about the action of radiation on any of these components. Bromobenzene [2] has been shown to yield hydrogen bromide when irradiated with X-rays, and pyridine [3,4] and aniline [4,5] are slowly converted into unknown products by other forms of ionising radiation. In this paper some of the products formed in the systems pyridine–bromobenzene and aniline–bromobenzene are reported.

From an equimolecular mixture of pyridine and bromobenzene the weight of the precipitated pyridine hydrobromide showed that $G(\mathrm{HBr}) = 5{\cdot}5$. From the filtrate, a mixture of 2-, 3-, and 4-phenylpyridine was isolated, with $G(\text{phenylpyridines}) = 1{\cdot}2$, apparently in the approximate ratio of 7 : 2 : 1. Although this is somewhat different from the isomer ratios reported in the phenylation of pyridine by benzoyl peroxide

[1] Cf. Collinson and Swallow, *Quart. Rev.*, 1955, **9**, 311; *Chem. Rev.*, 1956, **56**, 471; Tolbert and Lemmon, *Radiation Res.*, 1955, **3**, 52.
[2] Schuler and Hamill, *J. Amer. Chem. Soc.*, 1952, **74**, 6171.
[3] Rubin, U.S. Atomic Energy Commission Report NP-5135 (1954); *Nuclear Sci. Abs.*, 1954 **8**, No. 3698.
[4] Kailan, *Sitzungsber. Akad. Wiss. Wien*, 1926, IIa, **135**, 611.
[5] Chapiro, *J. Chim. phys.*, 1950, **47**, 764.

decomposing thermally to yield phenyl radicals (54, 32, and 14%, or 58, 28, and 14%) [6,7] or by the Gomberg reaction (46, 43, and 11% respectively),[6] the quantities of the isomers are in the same order. Under the influence of γ-radiation bromobenzene presumably undergoes homolysis; $PhBr \rightsquigarrow Ph\cdot + Br\cdot$, and the resulting phenyl radicals substitute the pyridine nucleus, hydrogen atoms being removed by the bromine atoms. Since, however, $G(HBr) > G$(phenylpyridines), other products must also be formed. The other reactions are unknown: they may be concerned with the breakdown of the aromatic or heterocyclic rings, since benzene, when irradiated, gives gaseous and polymeric products.[8]

From an irradiated equimolecular mixture of aniline and bromobenzene, aniline hydrobromide with $G(HBr) = 5{\cdot}9$, 2- and 4-aminodiphenyl with G(aminodiphenyls) $= 1{\cdot}7$, and azophenine with G value 0·46 (based on slightly impure material) were isolated, and traces of other coloured products were formed. We were unable to detect azophenine in a sample of pure aniline after irradiation and this compound is presumably formed by attack of the radicals derived from the bromobenzene on the amino-group of the aniline, resulting in dehydrogenation. Azophenine has previously been obtained from aniline or its salts by the action of iodic acid,[9] lead dioxide or manganese dioxide,[10] graphitic oxide,[11] or active carbon in the presence of oxygen,[11] as well as by electrolysis [12] and sunlight.[13] If the azophenine is assumed to arise according to the stoicheiometric equation, $5C_6H_5\cdot NH_2 \longrightarrow C_{30}H_{24}N_4 + NH_3 + 8H$, and the liberated hydrogen to react wholly with bromine atoms liberated from bromobenzene to form hydrogen bromide, then this reaction should result in the formation of hydrogen bromide with a G value of $0{\cdot}46 \times 8 = 3{\cdot}68$. The reaction, $Ph\cdot NH_2 + PhBr \longrightarrow HBr + Ph\cdot C_6H_4\cdot NH_2$, would result in the liberation of hydrogen bromide with a G value of 1·7, making a total of 5·38, not greatly less than the found value of 5·9. Spectroscopic results suggested that the 2- and 4-aminodiphenyl were present in approximately equal amount, with $<1\%$ of the 3-isomer. The literature appears to contain few reliable, quantitative data on reactions such as the phenylation of aniline; but the formation of mainly *ortho*- and *para*-isomers is to be expected in radical substitution in aromatic amines and phenols.[14] Irradiation of a mixture of aniline and bromobenzene in a molecular ratio of 1 : 4 gave the same products with $G(HBr) = 6{\cdot}7$ and G(aminodiphenyls) $= 1{\cdot}6$.

There thus appears to be no definite evidence against the formation of the observed products in the two systems studied by the radical reactions postulated, although excited-molecule reactions may be possible. If the suggested mechanism is correct, 2-, 3-, and 4-bromodiphenyl should also be produced. In the experiments with pyridine and aniline we did not look for these compounds, as we have shown them to be produced by γ-irradiation of bromobenzene alone. We hope, however, to publish full details of the latter work, together with further discussions of the isomer ratio in a later paper.

Experimental

Arrangements for Irradiations and Dosimetry.—The radiation unit was somewhat similar in design and operation to that described by Gibson and Pearce.[15] The irradiation vessels, of borosilicate glass, varied from test-tubes and small round-bottomed flasks for small samples to annular vessels, made to fit around the source tube, for larger samples. The dose-rate available

[6] Hey, Stirling, and Williams, *J.*, 1955, 3963.
[7] Dannley and Gregg, *J. Amer. Chem. Soc.*, 1954, **76**, 2997.
[8] Henri, Maxwell, White, and Peterson, *J. Phys. Chem.*, 1952, **56**, 153: Manion and Burton, *ibid.*, p. 560; Gordon, Van Dyken, and Donmini, *ibid.*, 1958, **62**, 20.
[9] Ostrogovich and Silbermann, *Chem. Zentr.*, 1908, I, 266.
[10] Börnstein, *Ber.*, 1901, **34**, 1268.
[11] Carter, Moulds, and Riley, *J.*, 1937, 1305.
[12] Szarvasy, *J.*, 1900, **77**, 207.
[13] Gibbs, *J. Amer. Chem. Soc.*, 1912, **34**, 1190.
[14] Dermer and Edmison, *Chem. Rev.*, 1957, **57**, 77; Augood and Williams, *ibid.*, p. 123.
[15] Gibson and Pearce, *Chem. and Ind.*, 1957, 613.

XUM

for each type of irradiation vessel was determined by use of the ferrous–ferric system, the concentration of the ferric ion in the irradiated solution being estimated by measurement of the optical density at 3050 Å, using a Hilger Uvispec Spectrophotometer, and a G value of 16·0 for the oxidation. The dose received by an organic system was taken as that absorbed by an equal volume of the aqueous dosimeter in the same vessel multiplied by the specific gravity of the organic liquid. The electron-density of the medium was not taken into account, as this is unnecessary for γ-radiation unless high accuracy is required.

Compounds to be irradiated were purified before use.

Irradiation of an Equimolecular Mixture of Pyridine and Bromobenzene.—A mixture of pyridine (126 g.) and bromobenzene (250 g.) was irradiated for 117 hr. (total dose $1{\cdot}84 \times 10^{23}$ ev), then diluted with ether. The precipitated pyridine hydrobromide (2·67 g.) was filtered off, the filtrate was washed with water and dried, and the bulk of the pyridine and bromobenzene were removed by distillation under reduced pressure. The residue was extracted with 17% hydrochloric acid, and the extract was basified and extracted with ether. The latter extract was dried and distilled, giving a mixture of phenylpyridines, b. p. 150°/10 mm. (0·55 g.). By fractional crystallisation (Haworth, Heilbron, and Hey's method [16]) the mixed picrates derived from this base yielded (*a*) yellow, rhombic prisms, m. p. 175—176°, (*b*) yellow needles, m. p. 159—160°, and (*c*) orange needles, m. p. 195—196°, which were shown, by mixed m. p. determinations, to be identical with samples of the picrates of 2-, 3-, and 4-phenylpyridine, respectively, prepared by Haworth, Heilbron, and Hey's method. Spectroscopic determination [6, 17] of the composition of the base mixture, on the assumption that it contained only 2-, 3-, and 4-phenylpyridine, showed these isomers to be present in the approximate ratios of 7 : 2 : 1. The phenylpyridine mixture was slightly impure (Found: C, 83·7; H, 6·0. Calc. for $C_{11}H_9N$: C, 85·15; H, 5·8%), the amount being small, so the accuracy of the result is uncertain. In particular, traces of dipyridyls might be present.

Irradiation of an Equimolecular Mixture of Aniline and Bromobenzene.—A mixture of aniline (128 g.) and bromobenzene (216 g.) was irradiated for 136 hr. (total dose $1{\cdot}83 \times 10^{23}$ ev) during which precipitation of aniline hydrobromide (3·14 g.) began and this was completed by the addition of dry ether (1 l.) after the irradiation. The nature of the precipitate was confirmed by conversion into aniline picrate (mixed m. p.). The ethereal filtrate was washed with water and dried, and the ether and the bulk of the aniline and bromobenzene were removed by distillation (water-bath/reduced pressure). An ethereal solution of the residue was extracted several times with 17% hydrochloric acid (total volume 200 ml.). The combined acid extracts were diluted with water and the resulting dark precipitate A (0·52 g.) was collected, washed with water, and dried in a vacuum-desiccator. The filtrate was basified with 40% sodium hydroxide solution and extracted with ether. The ether was removed from the dried (Na_2SO_4) extract, and the residue was heated at 100°/15 mm. to free it from volatile material. A solution of the resulting brown oil (6·35 g.) in light petroleum (b. p. 40—60°)–benzene (3 : 2) was chromatographed on Peter Spence Grade 0 alumina (160 g.). Development with light petroleum (b. p. 40—60°)–benzene (1 : 1) yielded a red oil which, on distillation, gave aniline, b. p. 100° (bath-temp.)/15 mm., followed by a base B (0·9 g.), b. p. 145° (bath-temp.)/0·5 mm., which slowly crystallised. Further development with benzene yielded more aniline. Development with chloroform yielded, on one occasion, an oil (0·3 g.), b. p. 145° (bath-temp.)/15 mm. (Found: C, 77·5; H, 7·65%). The latter figures are close to those required by aniline, but the b. p. did not agree and no picrate or hydrochloride could be obtained from the oil, the light absorption of which was weaker than that of aniline. Unfortunately we were unable to isolate the oil in subsequent experiments.

By fractional crystallisation of the hydrochloride of base B from benzene, two compounds were obtained:

(i) The less soluble fraction (which could also be sublimed out of the mixture) consisted of 4-aminodiphenyl hydrochloride, and basification yielded 4-aminodiphenyl which, when recrystallised from light petroleum (b. p. 40—60°), had m. p. 53° (Found: C, 85·1; H, 6·6. Calc. for $C_{12}H_{11}N$: C, 85·2; H, 6·5%) and afforded an acetyl derivative, m. p. 170° (Found: C, 79·25; H, 6 55. Calc. for $C_{14}H_{13}ON$: C, 79·6; H, 6·15%).

(ii) The more soluble fraction consisted of 2-aminodiphenyl hydrochloride, m. p. 180°, and

[16] Haworth, Heilbron, and Hey, *J.*, 1940, 349.

[17] Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds," Wiley, New York, 1951, p. 29; Cadogan, Hey, and Williams, *J.*, 1954, 794.

on basification yielded 2-aminodiphenyl, m. p. 49° (Found: C, 85·4; H, 6·4%), which gave an acetyl derivative, m. p. 120° (Found: C, 79·35; H, 6·45%).

These compounds were identified by direct comparison of m. p. and of ultraviolet spectra with authentic samples, the spectroscopic constants being tabulated.

	$\lambda_{max.}$ (Å)	ε	$\lambda_{min.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε
2-Aminodiphenyl (authentic)	2300	10,360	2750	1861	3000	3738
,, (from irradiation)	2300	10,320	2750	1840	3000	3654
4-Aminodiphenyl (authentic)	2175	9311	2375	2317	2800	13,930
,, (from irradiation)	2175	9265	2375	2265	2800	13,470

We were unable to isolate 3-aminodiphenyl from material B, but, on the assumption that the latter contained only the three isomeric aminodiphenyls, its composition was determined spectroscopically, following the general methods described by Cadogan, Hey, and Williams, and Friedel and Orchin,[17] to be 50·5, 1·0, and 48·5% of 2-, 3-, and 4-aminodiphenyl respectively.

A solution of the precipitate A in benzene–chloroform (1 : 1) was chromatographed on alumina. The first material to be eluted crystallised from ethyl acetate as red plates with a purplish iridescence, m. p. 253° [Found: C, 81·65; H, 5·25; N, 12·35%; *M* (Rast), 409. Calc. for $C_{20}H_{24}N_4$: C, 81·8; H, 5·45; N, 12·75%; *M*, 440]. The identity of this with azophenine (m. p. 253°) was shown by a mixed m. p. (253°) and by comparison of its spectrum (in ethyl acetate) with that of azophenine prepared by Ruggli and Buchmeier's method,[18] the following values being obtained:

	$\lambda_{max.}$ (Å)	ε	$\lambda_{min.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε
Azophenine (from irradiation)	2900	25,770	3300	7026	3800	16,820
,, (authentic)	2900	25,690	3300	7008	3800	16,800

The material dissolved in concentrated sulphuric acid to a deep purple solution, which became red on dilution or deep blue when heated. Further development with chloroform eluted the bulk of the original material, but the product was darker than, although otherwise indistinguishable from, the initial eluate.

Irradiation of a 1 : 4 *Molar Mixture of Aniline and Bromobenzene.*—A mixture of aniline (48 g.) and bromobenzene (337 g.) when irradiated for 160 hr. (total dose $2·15 \times 10^{22}$ ev) gave aniline hydrobromide (4·15 g.). 2- and 4-Aminodiphenyl (0·74 and 0·25 g., respectively) were isolated by chromatography on alumina, the former being eluted first (along with aniline) by light petroleum–benzene (7 : 3).

We thank the United Kingdom Atomic Energy Authority (Research Group, Harwell) for financial support, including the provision of a research assistantship (to P. S. T.), and for permission to publish this paper; also Professor G. R. Clemo, F.R.S., Dr. W. Wild, and Mr. J. Wright for their interest and help in the initiation of this work.

Department of Chemistry, King's College (University of Durham),
Newcastle upon Tyne, 1. [*Received, May 27th*, 1958.]

[18] Ruggli and Buchmeier, *Helv. Chim. Acta*, 1945, **28**, 850.

XUM

941. *The Chemical Effects of γ-Radiation on Organic Systems. Part II.* The Action of Radiation on Benzyl Alcohol Alone or Mixed with Acetone or Bromobenzene.*

By G. A. Swan and D. Wright.

Irradiation of benzyl alcohol with γ-rays gave rise to benzaldehyde, dibenzyl, 1 : 2-diphenylethanol, and *meso*- and racemic hydrobenzoin. In the presence of acetone, the last two compounds were produced in considerably greater energy yield. The products formed by the irradiation of a mixture of benzyl alcohol and bromobenzene were also investigated.

The most important contribution to the radiation chemistry of alcohols in the absence of water is McDonell and Newton's intensive study [1] of α-particle irradiation of aliphatic alcohols. By various analytical methods they established that the main organic products were aldehydes and α-glycols, relatively small amounts of hydrocarbons and ethers being formed. McDonell and Gordon [2] investigated the effect of γ-radiation on methanol; Skraba, Burr, and Hess [3] studied the decomposition of the same compound containing ^{14}C under the influence of its own β-rays; other workers have used α-particles [4] and *X*-rays or electrons.[5] Aldehydes are also known to be formed by the photolysis of alcohol vapours,[6] but in addition the production of ethylene glycol by photolysis of methanol vapour at low temperature has been reported.[7]

We studied the action of γ-radiation on benzyl alcohol, partly because the chemical reactivity of this compound differs somewhat from that of the purely aliphatic alcohols and partly because we thought that the products should be easier to isolate in this case. Also Chapiro [8] had measured the radical formation on irradiation of various types of compounds with γ-rays and had obtained the following values, taking the radical production from benzene as unity: *cyclo*hexane 4, ether 7, aniline 20, acetone 35, chloroform 50, alcohols 50—80, benzyl alcohol, butylamine, and benzylamine 80, and carbon tetrachloride 200. Thus benzyl alcohol appeared to be one of the more sensitive organic compounds towards radiolysis. Although we irradiated the benzyl alcohol for periods of nearly a week, only approximately 1% of it was converted into other products. Nevertheless, by the use of classical and chromatographic methods, we were able to isolate benzaldehyde, dibenzyl, 1 : 2-diphenylethanol, dibenzyl ether, and the two stereoisomeric hydrobenzoins, either in the free state or as crystalline derivatives. It was, however, clear that our separation was far from quantitative and we therefore decided to determine the yield of each product by the isotope-dilution method.

As we wished to determine the yield of each of the several products in one experiment, we labelled the benzyl alcohol isotopically and added a known weight of non-isotopic carrier after irradiation, rather than *vice versa*, despite the fact that we required a large amount of the benzyl alcohol. We chose ^{14}C as the isotope on account of the great dilution in which it can be determined (by the gas-counting method on $^{14}CO_2$). Our material was thus necessarily of very low specific activity and the effect of the soft β-rays emitted by the ^{14}C would be negligible compared with that due to the γ-radiation. Actually benzyl

* Part I, preceding paper.

[1] McDonell and Newton, *J. Amer. Chem. Soc.*, 1954, **76**, 4651.
[2] McDonell and Gordon, *J. Chem. Phys.*, 1955, **23**, 208.
[3] Skraba, Burr, and Hess, *ibid.*, 1953, **21**, 1296.
[4] McLennan and Patrick, *Canad. J. Res.*, 1931, **5**, 470; Kailan, *Sitzungsber. Akad. Wiss. Wien*, 1931, IIa, **140**, 419; *Monatsh.*, 1913, **34**, 1269; Breger, *J. Phys. Colloid Chem.*, 1948, **52**, 551.
[5] Bakh and Sorokin, *Sbornik Rabot Radiatsionnoĭ Khim., Akad. Nauk S.S.S.R.*, 1955, 163; *Chem. Abs.*, 1956, **50**, 4649; Bach, Proc. Internat. Conference, Peaceful Uses of Atomic Energy, Geneva, 1955, United Nations, New York, 1956, Vol. VII, p. 538.
[6] Patat and Hoch, *Z. Elektrochem.*, 1935, **41**, 494.
[7] Phibbs and Darwent, *J. Chem. Phys.*, 1950, **18**, 495.
[8] Chapiro, *J. Chim. phys.*, 1950, **47**, 764.

XUM

alcohol (275 ml.) containing ^{14}C in the alcohol group, of specific activity approximately 100 μc/mole, was irradiated at room temperature, then divided into a number of aliquot parts, to which accurately known weights of each pure, inactive product being assayed were added. A pure sample of this compound (or a crystalline derivative) was then isolated and burnt, and the specific activity of the resulting carbon dioxide was measured. It was thus possible to calculate the weight of this compound present in the irradiation mixture: the results are shown in Table 1.

TABLE 1. *Yields of products from γ-irradiation of* 275 *ml. of* [^{14}C]*benzyl alcohol* (*total dose* $1{\cdot}37 \times 10^{23}$ ev).

Compound estimated	Wt. of carrier (mg.)	Activity of CO_2 (counts/min.) *	Wt. of product (mg.)	*G* (product)
Benzyl alcohol	—	1860	—	—
Benzaldehyde	454	869	398	1·32
,, (control)	82·9	920	81·2	
Benzaldehyde dibenzyl acetal	883·1	16·7	<8	—
Dibenzyl	267·9	578	120·8	0·29
1 : 2-Diphenylethanol	280·1	968	304	0·68
Dibenzyl ether	1698	100·5	97	—
meso-Hydrobenzoin	234·8	535	95·0	0·20
Racemic hydrobenzoin	243·8	566	106·7	0·22

* For compounds isolated as derivatives these values have already been multiplied by an appropriate factor so that they represent the activities of CO_2 which would have been obtained if the pure compounds named in the left-hand column of the Table had been burnt.

From these it is seen that 1 : 2-diphenylethanol is produced in energy yield about half that of benzaldehyde, and that dibenzyl comes next in order of quantity. *meso*- and Racemic hydrobenzoin were formed in approximately equal amounts. The formation of these products can be explained on the assumption that under the influence of γ-radiation benzyl alcohol can break down in two different ways:

$$Ph{\cdot}CH_2{\cdot}OH \rightsquigarrow Ph{\cdot}CH(OH){\cdot} + H{\cdot} \quad (a)$$

and

$$Ph{\cdot}CH_2{\cdot}OH \rightsquigarrow Ph{\cdot}CH_2{\cdot} + HO{\cdot} \quad (b)$$

The resulting radicals could then give the observed products as follows:

$$2Ph{\cdot}CH(OH){\cdot} \longrightarrow [Ph{\cdot}CH(OH)]_2$$

$$2Ph{\cdot}CH_2{\cdot} \longrightarrow [CH_2Ph]_2$$

$$Ph{\cdot}CH(OH){\cdot} + Ph{\cdot}CH_2{\cdot} \longrightarrow Ph{\cdot}CH_2{\cdot}CHPh{\cdot}OH$$

The benzaldehyde might arise in various ways, such as the following:

$$2Ph{\cdot}CH(OH){\cdot} \longrightarrow Ph{\cdot}CHO + Ph{\cdot}CH_2{\cdot}OH$$

or by hydrogen abstraction by hydrogen atoms or hydroxyl radicals. From purely aliphatic alcohols, aldehydes and glycols are the main products presumably because the alkyl radicals are much less stable than the benzyl radical and fission (*a*) predominates over (*b*), the oxygen of the R·CH(OH)· radical helping to stabilise it. Thus McDonell and Newton [1] found that the products formed by radiolysis of aliphatic alcohols were consistent with the assumption that the principal bond rupture occurred at bonds joining groups (with ease H > Et > Me) to the $CH_2{\cdot}OH$ carbon atom, with little tendency for fission of the C–O bond (as seen by the very small production of ethers and of hydrocarbons containing the same number of carbon atoms as the alcohols). They worked in a totally enclosed system and attempted to determine all (including gaseous) products and to work out an oxidation–reduction balance, as well as a mass balance. However, there remained some water and hydrogen for which they could not account. On the other hand Coleby, Keller, and Weiss,[9] who investigated the effect of *X*-rays on various steroids in

[9] Coleby, Keller, and Weiss, *J.*, 1954, 66.

methanol, suggested that radiolysis of the C–O bond occurred in methanol. More recently Burr,[10] from a study of the radiolysis of five different deuterated ethanols with ^{60}Co γ-rays, concluded that the hydrogen production proceeded by a primary (rate-determining) radical process:

$$CH_3{\cdot}CH_2{\cdot}OH \longrightarrow CH_3{\cdot}CH(OH){\cdot} + H{\cdot}$$

From the deuterium content of the evolved hydrogen he concluded that the ensuing (rapid) abstraction affects principally the hydroxyl-hydrogen, with a small amount from the methyl group:

$$H{\cdot} + CH_3{\cdot}CH_2{\cdot}OH \longrightarrow CH_3{\cdot}CH_2{\cdot}O{\cdot} + H_2\ (80\text{—}90\%)$$
$$H{\cdot} + CH_3{\cdot}CH_2{\cdot}OH \longrightarrow {\cdot}CH_2{\cdot}CH_2{\cdot}OH + H_2\ (10\text{—}20\%)$$

The glycol could then be formed by combination of $CH_3{\cdot}CH(OH){\cdot}$ radicals, while the aldehyde could arise from either the latter or $CH_3{\cdot}CH_2{\cdot}O{\cdot}$ radicals and is therefore produced in greater amount (Burr found the amounts of aldehyde and glycol formed were in the ratio 2·2 : 1·05). For benzyl alcohol we found no conclusive evidence of a third type of radiolysis (*c*):

$$Ph{\cdot}CH_2{\cdot}OH \rightsquigarrow Ph{\cdot}CH_2{\cdot}O{\cdot} + H{\cdot} \quad \ldots\ldots\ldots\ (c)$$

However, we cannot rule out the possibility that part of the benzaldehyde might have arisen from the $Ph{\cdot}CH_2{\cdot}O{\cdot}$ radicals. For ethanol irradiated with *X*-rays or electrons, Bakh and Sorokin [5] showed that the energy yield of aldehyde increased in the presence of oxygen; but we have not studied this effect in the case of benzyl alcohol.

It was of interest to know whether acetal formation could be achieved in the absence of acid catalysts, under the influence of γ-radiation, and we therefore estimated the benzaldehyde dibenzyl acetal in the irradiation product of benzyl alcohol. A preliminary experiment showed that this acetal could be recovered unchanged after its ethereal solution had been treated with sodium hydrogen sulphite solution, so we removed the free benzaldehyde from the irradiation mixture under similar conditions before adding carrier acetal. The acetal which we isolated, however, was almost inactive, so we concluded that no appreciable amount of benzaldehyde had been converted into its dibenzyl acetal. We are, however, studying other carbonyl-addition reactions to see whether they are influenced by γ-radiation.

The status of the dibenzyl ether is uncertain and we regard it as very questionable whether it is a true irradiation product. The small amount which we isolated after isotope dilution was probably not quite pure, so the low activity recorded may have been due to radioactive contamination. It is known that when benzyl alcohol is heated for 5 days in a sealed glass tube at 210—215°, about 10% conversion into dibenzyl ether occurs.[11] As the working up of our mixture included distillation under water-pump vacuum it seems not impossible that traces of the ether might have thus been formed.

The relative proportions of *meso*- and racemic hydrobenzoin formed are of some interest, particularly as it had been reported [12] that mainly the *meso*-form results on ultraviolet irradiation of benzyl alcohol in acetone, the mechanism again presumably involving $Ph{\cdot}CH(OH){\cdot}$ radicals. The two isomers were therefore determined in separate portions of the irradiation mixture by addition of known weights of the respective inactive carriers. As there was the possibility, at any rate in the case of racemic hydrobenzoin, that part of the material might be present as a benzylidene derivative (cyclic acetal), the mixture was refluxed with hydrochloric acid to ensure that the carrier was effectively mixed. To avoid possible, subsequent loss of hydrobenzoin due to re-acetalisation, the benzaldehyde was removed by bisulphite treatment. The mixture of hydrobenzoins was isolated by chromatography and was separated into the *meso*- and the racemic form *via* the dibenzoates, as

[10] Burr, *J. Phys. Chem.*, 1957, **61**, 1477.
[11] Lachman, *J. Amer. Chem. Soc.*, 1923, **45**, 2356.
[12] Ciamician and Silber, *Ber.*, 1910, **43**, 945.

XUM

described by Meerwein and Schmidt.[13] To test whether the racemic was converted into the (presumably) more stable *meso*-form during working up, in the case of that portion of the reaction mixture to which the racemic form had been added, we isolated not only this, but also the *meso*-form (as its dibenzoate) and measured its activity. If part of the racemic form had been converted into the *meso*-form, then the specific activity of the carbon dioxide produced by combustion of the *meso*-hydrobenzoin dibenzoate should be less than one-half of that of the original benzyl alcohol. As seen from Table 2, the activity of this *meso*-material was one half that of the benzyl alcohol (within the limits of experimental error), showing absence of interconversion.

TABLE 2.

	Activity of CO_2 formed by combustion (counts/min.)
Benzyl alcohol	1860
meso-Hydrobenzoin dibenzoate (Calc.)	930
,, ,, (Found)	912

Ciamician and Silber [12] reported that the action of light on a solution of benzyl alcohol in acetone yields *meso*-hydrobenzoin, with very little of the racemic isomer. We therefore studied the γ-irradiation of an equimolecular mixture of acetone and radioactive benzyl alcohol, the results being shown in Table 3. The only irradiation products estimated were the two hydrobenzoins; but in each of the two isotope dilution experiments (that is one to which *meso*- and one to which racemic carrier was added) *both* isomers were isolated. The results show that, in each case, the specific activity of the " undiluted " hydrobenzoin is, in fact, equal to that of the benzyl alcohol, thus confirming that interconversion of isomers has not occurred during the working up. It is also seen that the *meso*- and the racemic form are produced in approximately equal amounts, in contrast to the results reported for the light-induced reaction. It would be interesting to apply our method of analysis to the latter case as a check on Ciamician and Silber's results. It is unlikely although not impossible that the racemic might be converted into the *meso*-form under the influence of ultraviolet radiation.

TABLE 3. *γ-Irradiation of an equimolecular mixture of [^{14}C]benzyl alcohol and acetone of total volume 275 ml. (total dose $1{\cdot}25 \times 10^{23}$ ev).*

Compound	Wt. of carrier (mg.)	Activity of CO_2 (counts/min.) *	Wt. of product (mg.)	G (product)
Benzyl alcohol	—	1949	—	—
meso-Hydrobenzoin	194·5	1236	337	0·76
Racemic hydrobenzoin	266·3	1077	330	0·75
" Undiluted " *meso*-hydrobenzoin	—	1956	—	—
" Undiluted " racemic hydrobenzoin	—	1904	—	—

* In the case of *meso*-hydrobenzoin, the dibenzoate was burnt; but the values in this column have already been multiplied by two so that they represent the activities of CO_2 which would have been obtained if the hydrobenzoin itself had been burnt.

In the case of pure benzyl alcohol, the hydrobenzoins were produced with a G value of 0·42, while in acetone solution the value was 1·51. The reason for this may be that acetone is a good hydrogen-acceptor.

We also investigated the irradiation of a mixture of benzyl alcohol and bromobenzene; hydrogen bromide and benzaldehyde were produced with G values of 2·9 and 0·76 respectively. Benzaldehyde dibenzyl acetal, racemic benzylidenehydrobenzoin (G value 0·24), and dibenzyl ether were also isolated; but we do not regard the ether as a true irradiation product. It seems that benzyl bromide is formed during the irradiation and that this probably reacts with benzyl alcohol, either then or during the subsequent working-up. Thus, when a solution of hydrogen bromide in benzyl alcohol had been irradiated, dibenzyl ether was isolated; but a similar solution which was kept without irradiation for the same

[13] Meerwein and Schmidt, *Annalen*, 1925, **444**, 221.

length of time yielded the ether in not greatly reduced yield. Also, the amount of dibenzyl ether isolated from the irradiated benzyl alcohol–bromobenzene mixture was much reduced when the mixture was treated with sodium hydrogen sulphite solution before distillation, and the residue left after removal of the bromobenzene and benzyl alcohol was then not completely soluble in light petroleum containing 2% of benzene. This was thought to be due to reaction of benzyl bromide with the sodium hydrogen sulphite solution. Dibenzyl was apparently not formed by irradiation of benzyl alcohol in the presence of bromobenzene.

As we were unable to isolate the products formed from the phenyl radicals which had presumably been liberated we irradiated an equimolecular mixture of benzyl alcohol and [^{14}C]bromobenzene; by subsequent addition (as inactive carrier) of compounds which we thought might be formed we showed the formation of diphenyl (*G* value 0·18), but diphenylmethane appeared to be absent. The greater part of the material of higher boiling point than bromobenzene remained in gummy fractions which failed to crystallise.

Experimental

Arrangements for the irradiations and spectroscopic measurements were as described in Part I. The radioactivity measurements were all made by the gas-counting method on $^{14}CO_2$ as described by Swan.[14] The alumina used for chromatography was supplied by Savory and Moore.

Isolation of Products Formed by Irradiation of Benzyl Alcohol.—Commercial benzyl alcohol was washed several times with 40% sodium hydrogen sulphite solution followed by sodium carbonate solution, then dried and fractionated. The purified alcohol (275 ml.) was irradiated for 140 hr. (total dose $1·69 \times 10^{23}$ ev). The benzaldehyde formed was extracted by shaking it with 40% sodium hydrogen sulphite solution (3×40 ml.). The extract was boiled with 5N-sulphuric acid, and the benzaldehyde was distilled in steam. With Brady's reagent the distillate gave benzaldehyde 2 : 4-dinitrophenylhydrazone (0·424 g.).

The benzyl alcohol layer was washed with sodium carbonate solution, dried, and distilled at 12 mm. through a fractionating column until a residue of ~4 ml. remained. A solution of this residue in light petroleum (b. p. 40—60°; 200 ml.) containing benzene (2%) was chromatographed on alumina (80 g.), fractions of 50 ml. being collected. Elution was continued with light petroleum containing benzene (5%). The first few fractions yielded crystalline dibenzyl, identified by its m. p. and ultraviolet spectrum and by conversion into the tetranitro-derivative, m. p. 163—164°. A mixture of the latter with authentic 2 : 2′ : 4 : 4′-tetranitrodibenzyl [15] (m. p. 164—165°) melted at 163°.

Further elution of the chromatogram with light petroleum containing benzene (5%) yielded dibenzyl ether, b. p. 150° (bath-temp.)/1 mm., n_D^{20} 1·5648 (for pure dibenzyl ether, 1·5625). Elution was continued with benzene, then with chloroform. The first chloroform fraction contained mainly racemic deoxybenzoin and this was followed by benzyl alcohol. The former, when recrystallised from light petroleum (b. p. 60—80°), had m. p. 67° (Found: C, 84·8; H, 7·2. Calc. for $C_{14}H_{14}O$: C, 84·8; H, 7·05%), identified by comparison with an authentic sample prepared by Gerrard and Kenyon's method.[16] The phenylurethane had m. p. 91° and the 3 : 5-*dinitrobenzoate* m. p. 184—185° (Found: C, 64·3; H, 4·45. $C_{21}H_{16}O_6N_2$ requires C, 64·3; H, 4·1%). The alcohol could be isolated (as this derivative) from fractions also containing benzyl alcohol by removing the latter by distillation in bulbs and treating the residue with 3 : 5-dinitrobenzoyl chloride in pyridine.

Finally, by elution of the chromatogram with chloroform containing methanol (25%), a mixture of *meso*- and racemic hydrobenzoin was obtained. These were separated as the dibenzoates as described in the experiment using radioactive benzyl alcohol.

In a similar experiment in which the bisulphite treatment was omitted, in addition to the products mentioned above, benzaldehyde dibenzyl acetal, b. p. 220° (bath-temp.)/1 mm. (0·8 g.), was isolated. This was eluted along with dibenzyl ether and separated by distillation. It is almost certain that this acetal had been formed during the distillation rather than during the irradiation.

Irradiation of [^{14}C]*Benzyl Alcohol.*—The radioactive alcohol was prepared in almost

[14] Swan, *J.*, 1955, 1039.
[15] von Braun and Rawicz, *Ber.*, 1916, **49**, 799.
[16] Gerrard and Kenyon, *J.*, 1928, 2564.

theoretical yield by reduction of benz[^{14}C]oic acid (4 g., 300 μc) with lithium aluminium hydride (2·4 g., 2 mol.) in ether; it was diluted to 300 ml. with inactive benzyl alcohol, giving a product of specific activity of approximately 100 μc/mole. This (275 ml.) was irradiated for 121 hr. (total dose $1{\cdot}37 \times 10^{23}$ ev). The extra energy absorbed due to the radiation from the ^{14}C is negligible (approximately 10^{20} ev). A separate sample of the same benzyl alcohol was kept in the dark, without irradiation, for the same period, after which the benzaldehyde in it was determined (control value).

The irradiated material was divided into a number of separate (not all equal) portions, for assay of different products by isotope dilution. A carefully purified and weighed sample of the inactive compound the yield of which was to be determined was added to an appropriate portion of the benzyl alcohol. In the following description, however, the amount of inactive carrier mentioned is that which would have corresponded to the use of the full 275 ml. of the irradiated material in each case. In other words, the work was carried out on a smaller scale than is described from now on; but the yields shown in Table 1 correspond to 275 ml. of benzyl alcohol.

(i) Benzaldehyde. The irradiated benzyl alcohol was mixed with pure benzaldehyde (454 mg.). The aldehyde was then isolated by extraction with sodium hydrogen sulphite solution and was converted into the 2 : 4-dinitrophenylhydrazone (as described above) which when recrystallised from ethyl acetate had m. p. 234° and was used for the radioactivity measurements. The control value in the sample not irradiated was likewise determined.

(ii) Benzaldehyde dibenzyl acetal. The irradiated benzyl alcohol was washed with sodium hydrogen sulphite, then with sodium carbonate solution. Benzaldehyde dibenzyl acetal (883·1 mg.) was added and the bulk of the benzyl alcohol was removed by distillation. The residue was chromatographed (as above), the various fractions of the eluate being treated with Brady's reagent. Had any of the hydrobenzoin formed an acetal with benzaldehyde during the irradiation, it is likely that the product would have had similar adsorption on alumina to benzaldehyde dibenzyl acetal and hence been mixed with the latter. The very weak radioactivity of the benzaldehyde 2 : 4-dinitrophenylhydrazone, however, counts also against this acetalisation.

(iii) Dibenzyl. The irradiated benzyl alcohol was treated with dibenzyl (267·9 mg.). The dibenzyl was recovered as above, by making use of its very weak adsorption on alumina, and when recrystallised from methanol had m. p. 52° and was used as such for the radioactivity measurements.

(iv) 1 : 2-Diphenylethanol. The irradiated benzyl alcohol was treated with the alcohol (280·1 mg.), which was then recovered as described above and was recrystallised twice from light petroleum (b. p. 60—80°) containing benzene (5%); it had m. p. 67° and was assayed as such.

(v) Dibenzyl ether. The irradiated benzyl alcohol was treated with dibenzyl ether (1698 mg.) which was then recovered as described above. The isolated material had b. p. 150° (bath-temp.)/1 mm., n_D^{20} 1·559, and, although probably not quite pure, was used for the radioactivity measurements.

(vi) Racemic hydrobenzoin. *meso*- and Racemic hydrobenzoin were prepared by Meerwein and Schmidt's method.[13] The *meso*-form, when recrystallised from ethanol, had m. p. 135—136°. The three previously described forms of racemic hydrobenzoin (m. p. 95°, 104°, and 119—120°) were all encountered; but that of m. p. 119—120° was used as carrier in the isotope dilution experiment.

The irradiated benzyl alcohol was treated with racemic hydrobenzoin (243·8 mg.), then refluxed for 1 hr. with N-hydrochloric acid (200 ml.). The organic layer was washed with sodium hydrogen sulphite, followed by sodium carbonate solution, then dried and the benzyl alcohol was removed by vacuum-distillation. A solution of the residue in benzene was chromatographed on alumina (70 g.). The column was eluted with benzene and chloroform and the hydrobenzoin mixture was finally eluted with chloroform containing methanol (25%). A mixture of the hydrobenzoins, benzoyl chloride (1 g.), and pyridine (4 ml.) was kept at room temperature for 12 hr., then treated with water. The precipitated dibenzoate mixture was collected, dried, boiled with ethanol (8 ml.), and filtered hot. The solid left on the filter was *meso*-hydrobenzoin dibenzoate (100 mg.) and the filtrate on cooling deposited impure racemic hydrobenzoin dibenzoate, m. p. 125° (166 mg.). The latter was refluxed for 3 hr. with potassium hydroxide (100 mg.) in ethanol (4 ml.), and the product was isolated by distillation of the ethanol and addition of water. The m. p. of this racemic hydrobenzoin was raised to 95° by

XUM

recrystallisation from dilute acetic acid and finally to 119—120° from benzene–light petroleum (b. p. 60—80°). The last form was used for the radioactivity measurements. The *meso*-hydrobenzoin dibenzoate was recrystallised from acetic acid, affording needles, m. p. 244—245°, used for radioactivity measurements.

(vii) *meso*-Hydrobenzoin. The irradiated benzyl alcohol was treated with *meso*-hydrobenzoin (234·8 mg.) and this was then isolated as the dibenzoate, which was used for the radioactivity measurements.

Irradiation of an Equimolecular Mixture of [^{14}C]*Benzyl Alcohol and Acetone.*—The alcohol was prepared as described above; it was a fresh batch to obviate any possible spurious results due to impurities in the recovered material. The acetone was shaken for 20 hr. with potassium permanganate, from which it was then distilled and dried ($MgSO_4$). The mixture (275 ml.) was irradiated for 138 hr. (total dose $1{\cdot}25 \times 10^{23}$ ev) and divided into two portions, *meso*- or racemic hydrobenzoin being added to each severally. The mixture was then fractionated and the residue treated as described above for the isolation of the hydrobenzoin, both isomers being solated in each case.

In a blank experiment, in which a mixture of acetone and benzyl alcohol was kept for a week in the dark, no trace of hydrobenzoin could be detected.

Irradiation of a Mixture of Benzyl Alcohol and Bromobenzene.—(1) An equimolecular mixture of benzyl alcohol and bromobenzene (275 ml.) was irradiated for 120 hr. (total dose $1{\cdot}77 \times 10^{23}$ ev). The hydrogen bromide formed (0·70 g.) was extracted with water and titrated with standard alkali. The benzaldehyde was separated from the organic layer by treatment with sodium hydrogen sulphite solution in the way described under the irradiation of benzyl alcohol alone and yielded the 2 : 4-dinitrophenylhydrazone (0·770 g.). However, a similar experiment in which the mixture had been kept in the dark without irradiation for the same period yielded benzaldehyde 2 : 4-dinitrophenylhydrazone (0·134 g.), indicating that the weight of benzaldehyde formed by the radiation was 0·636 g.

The organic layer, after treatment with sodium hydrogen sulphite, was washed with alkali, dried, and distilled at 12 mm. through a fractionating column until a residue of ~6 ml. remained. The part of this which was soluble in light petroleum (b. p. 40—60°) containing benzene (2%) was chromatographed from this solvent on alumina (80 g.). For development the percentage of benzene was increased to 5. The earlier fractions yielded dibenzyl ether (0·4 g.), b. p. 150° (bath-temp.)/1 mm. (identified by infrared spectrum). The subsequent fractions yielded a solid which, when recrystallised from methanol, formed colourless crystals, m. p. 85° (0·2 g.), of racemic benzylidenehydrobenzoin (Found: C, 83·4; H, 6·5. Calc. for $C_{21}H_{18}O_2$: C, 83·4; H, 6·0%). This, on treatment with an acidified ethanolic solution of 2 : 4-dinitrophenylhydrazine, yielded benzaldehyde 2 : 4-dinitrophenylhydrazone. Its ultraviolet spectrum ($\lambda_{max.}$ 2575 Å, log ε 2·82; $\lambda_{min.}$ 2350 Å, log ε 2·14) was identical with that of a synthetic sample,[17] m. p. 85°, and no depression occurred on admixture.

(2) An irradiation similar to the above was performed, but the irradiated mixture was not treated with sodium hydrogen sulphite. It was washed with sodium carbonate solution, dried, and worked up otherwise as before. The residue from the distillation was completely soluble in light petroleum (b. p. 40—60°) containing benzene (2%). The earlier fractions from the chromatogram yielded: (*a*) dibenzyl ether (3 g.), b. p. 158°/11 mm., n_D^{20} 1·5648 (Found: C, 84·4; H, 7·4. Calc. for $C_{14}H_{14}O$: C, 84·6; H, 7·1%), the infrared spectrum being identical with that of dibenzyl ether; and (*b*) benzaldehyde dibenzyl acetal, b. p. 220° (bath-temp.)/11 mm. (Found: C, 83·05; H, 6·65. Calc. for $C_{21}H_{20}O_2$: C, 82·9; H, 6·6%), which with acidified, ethanolic 2 : 4-dinitrophenylhydrazine yielded benzaldehyde 2 : 4-dinitrophenylhydrazone.

(3) An experiment similar to the above in which the mixture was kept without irradiation, then worked up as before, yielded no residue after removal of the bromobenzene and benzyl alcohol by distillation.

(4) A 1 : 10 molar mixture (275 ml.) of benzyl alcohol and bromobenzene was irradiated for 168 hr. (total dose $2{\cdot}64 \times 10^{23}$ ev). Hydrogen bromide (1·0 g., *G* value 2·8) and benzaldehyde (0·46 g., *G* value 1) were formed and were estimated in an aliquot portion. The main bulk of the irradiated mixture was worked up as in (2) and yielded dibenzyl ether (1 g.) and benzaldehyde dibenzyl acetal (1·3 g.). No racemic benzylidenehydrobenzoin was isolated.

Irradiation of a Mixture of Benzyl Alcohol and Hydrobromic Acid (with A. F. Everard).—A mixture of benzyl alcohol (270 ml.) and 47% hydrobromic acid (2·7 ml.) was irradiated for

[17] Read, Campbell, and Barker, *J.*, 1929, 2305.

168 hr. (total dose $1{\cdot}70 \times 10^{23}$ ev), then washed with sodium carbonate solution, dried, and fractionated. Dibenzyl ether (1·18 g.) and benzaldehyde dibenzyl acetal (0·73 g.) were obtained and identified by infrared spectra. A similar mixture which had been kept in the dark, without irradiation, for the same period yielded dibenzyl ether (0·82 g.) and none of the acetal.

Irradiation of an Equimolecular Mixture of Benzyl Alcohol and [^{14}C]*Bromobenzene.*—[^{14}C]-Benzene was brominated as described for the preparation of bromobenzene by Gattermann.[18]

(1) The mixture (275 ml.) was irradiated for 134 hr. (total dose $1{\cdot}86 \times 10^{23}$ ev) and worked up as above. The mixture was distilled through a fractionating column and the benzyl alcohol was collected in several fractions, the specific activity of each being measured. However all were of very low activity. The residue (4 g.), b. p. >130°/2 mm., had an activity which suggested that it contained phenyl residues (0·4 g.). The chromatogram fractions containing dibenzyl ether and benzaldehyde dibenzyl acetal were distilled to remove these compounds; the residue was gummy and did not distil at 250°/1 mm. The specific activity of the residue corresponded with the presence of one phenyl residue to every 3—4 benzyl residues.

(2) Carrier diphenyl and diphenylmethane were added to aliquot parts of a similar mixture which had been irradiated for 120 hr. (total dose $1{\cdot}47 \times 10^{23}$ ev). The former was re-isolated by chromatography of the high-boiling residue and converted into 4-nitrodiphenyl,[19] m. p. 110—112°, the specific activity of which indicated that 67 mg. of diphenyl had been formed in the whole irradiation. Diphenylmethane was re-isolated by making use of its very weak adsorption on alumina and was converted into 2 : 2′ : 4 : 4′-tetranitrodiphenylmethane,[20] m. p. 168—169°, which was almost inactive.

We thank the United Kingdom Atomic Energy Authority (Research Group, Harwell) for generous financial support, including the provision of a research assistantship (to D. W.), and for permission to publish this paper.

Department of Chemistry, King's College (University of Durham),
Newcastle upon Tyne, 1. [*Received, May 27th,* 1958.]

[18] Gattermann, revised by Wieland, "Laboratory Methods of Organic Chemistry," Macmillan, London, 1937, p. 103.
[19] Bell, Kenyon, and Robinson, *J.*, 1926, 1239.
[20] Schöpff, *Ber.*, 1894, **27**, 2316.

---

942. *Infrared Spectra and the Polymorphism of Glycerides. Part V.* 1 : 2-Diglycerides.*

By D. Chapman.

The polymorphism of some 1 : 2-diglycerides has been investigated by means of infrared spectroscopy between 3500 and 670 cm.$^{-1}$. The spectra are discussed in terms of the packing of the hydrocarbon chains in the crystals and are compared with that of the 1 : 3-isomer.

Infrared spectroscopy has recently been applied to the study of the polymorphism of a variety of long-chain compounds including alcohols, esters, and glycerides.[1,2] It is here applied to the study of the polymorphism of some 1 : 2-diglycerides. Howe and Malkin[3] previously examined these glycerides by thermal and *X*-ray methods. It is of interest to see whether the spectra of these forms fit the general pattern already found for other types of glycerides, and to contrast the spectra with those of the 1 : 3-isomers.

Experimental.

The 1 : 2-diglycerides (laurin, myristin, palmitin, and stearin) were made by Mr. I. P. Freeman[4] of these laboratories. A sample of 1 : 2-dilaurin was also kindly presented by Dr. T. Malkin of Bristol University.

* Part IV, *J.*, 1958, 3186.

[1] Chapman, *J.*, 1956, 53, 2522; 1957, 2715.
[2] Chapman, 6th Internat. Spectroscopic Colloquium Symp., Amsterdam, 1956.
[3] Howe and Malkin, *J.*, 1951, 2663.
[4] Freeman and Pierce, unpublished work.

Experimental details were similar to those described in the earlier papers.[1] *X*-Ray results on the most stable form of each glyceride were in good agreement with those given by Howe and Malkin.[3] Two polymorphic forms were observed for each glyceride. Crystallisation from solvents gave the higher-melting forms. Re-solidification from the melt gave the lower-melting form. Holding the lower-melting form for many hours near its m. p. converted it into the higher-melting form.

Thermal data for the 1 : 2-diglycerides (Table) are in good agreement with those given by Howe and Malkin.[3]

Melting points.

	$\alpha_L = \alpha_M$	$\beta_L' = \beta_M$		$\alpha_L = \alpha_M$	$\beta_L' = \beta_M$
Dilaurin	19·7°	38·2°	Dipalmitin	49·7—50°	61°
Dimyristin	37·1	51·7	Distearin	59·9	71

Results and Discussion.

The spectra of the liquid and of each of the polymorphic forms of the four 1 : 2-diglycerides were obtained. Apart from the 1250 cm.$^{-1}$ region where the number of bands present increased with increasing chain length, the spectrum of a particular form bears a marked "family" resemblance to those of its homologues. Only the spectra of the liquid and the crystalline forms of 1 : 2-distearin are therefore discussed in detail (see Fig. 1).

Liquid State.—The spectrum is rather typical of that obtained from other glycerides in the liquid state. Prominent bands occur at 3407, 1743, 1463, 1418, 1374, 1240, 1166, 1116, 1097, 1054 and 720 cm.$^{-1}$.

Crystalline Forms.—First form. Solidification from the melt gives the first crystalline form, whose bands occur at 3385 and 1740 cm.$^{-1}$. The band previously at 1418 cm.$^{-1}$ shifts to 1416 cm.$^{-1}$ and that originally at 1166 shifts to 1178 cm.$^{-1}$. A series of bands occur in the 1250 cm.$^{-1}$ region, at 1342, 1329, 1309, 1290, 1272, 1253, 1234, 1214, and 1194 cm.$^{-1}$ spaced about 18 cm.$^{-1}$ apart. These bands probably arise from CH_2 wagging vibrations.[5] Strong bands also occur at 1104, 1062, and 1045 cm.$^{-1}$. The band at 720 cm.$^{-1}$ is single and increased in intensity.

When this form was heated to 59° and the spectrum scanned, the material was observed to melt and the spectrum of the liquid form was again obtained.

Second form. Crystallisation from solvent gave the second form, whose spectrum shows many differences from that of the first. Prominent bands occur at 3468, 1733, and 1709 cm.$^{-1}$. The band at 1416 cm.$^{-1}$ in the spectrum of the first form now shifts to 1423 cm.$^{-1}$. The bands in the 1250 cm.$^{-1}$ region have the same frequencies (within experimental limits) as for the first form, but the relative intensities of the bands are greatly altered. A doublet occurs at 1109 and 1092 cm.$^{-1}$, a strong band at 1066 cm.$^{-1}$, and weak bands at 1042, 1028, 958, 873, 886, 842, 810, and 758 cm.$^{-1}$. There are two components at 729 and 719 cm.$^{-1}$.

The spectrum of 1 : 3-distearin in its crystalline form is also shown in Fig. 1. The remarkable difference between the spectra suggests that the isomeric configuration of unknown diglycerides of this type may be easily deduced by means of their infrared spectra.

A line diagram showing the bands in the 1250 cm.$^{-1}$ region of the four glycerides is shown in Fig. 2. As is observed with anhydrous sodium soaps there is an empirical relation between the number of bands and the length of the aliphatic chain, *viz.*, the number of bands is equal to half the number of carbon atoms in the chain. Further, the frequency difference between the band of highest frequency and the next lower band is always less than the frequency difference between the other bands. This may be related tentatively to the presence of the α-methylene group, where the influence of the carbonyl group is greatest. The frequency difference between the remaining bands is approximately constant for each glyceride.

The lowest-melting forms of these glycerides have been designated [3] α-forms. Their infrared spectra support this designation, by analogy with the spectra of the α-forms of hydrocarbons, alcohols, and esters.[2] There is moreover a strong general resemblance

[5] Sinclair, McKay, and Jones, *J. Amer. Chem. Soc.*, 1952, **74**, 2570; Chapman, *J.*, 1958, 784.

between this type of spectrum and that of the lowest-melting form of saturated triglycerides, recently designated [1] an α_L-form. Two components occur at 729 and 719 cm.$^{-1}$ in the spectrum of the higher-melting form, as in the spectra of the forms previously

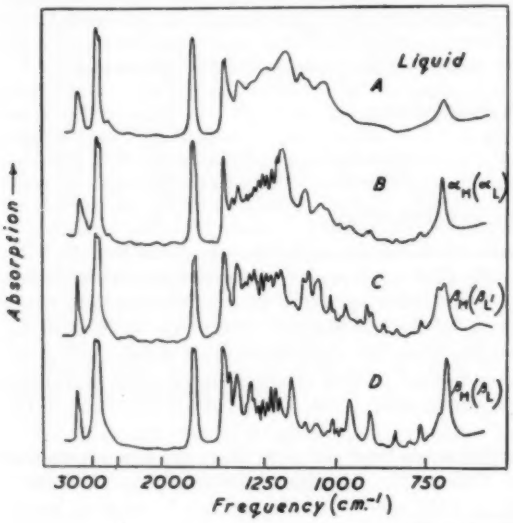


FIG. 1. *Infrared spectra of* (*A*, *B*, *C*) 1 : 2-*distearin and* (*D*) 1 : 3-*distearin.*

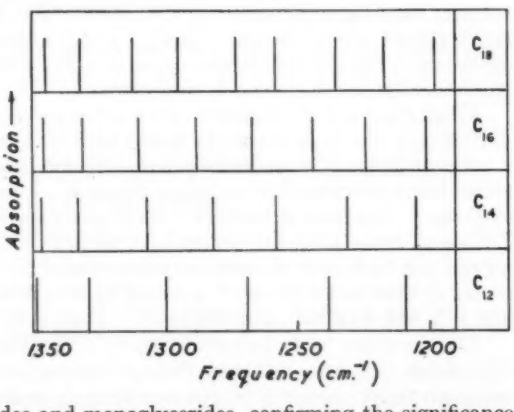


FIG. 2. *Line diagrams of infrared spectra of triglycerides in the* 1250 *cm.*$^{-1}$ *region.*

designated β_L' for saturated triglycerides and monoglycerides, confirming the significance of the general classification.[1] (The main *X*-ray short spacings are at 3·8 and 4·2 Å; cf. Lutton.[6])

We can deduce that the hydrocarbon chain packing in the $\alpha_L(\equiv\alpha_M)$-form of the 1 : 2-diglycerides is hexagonal, whilst in the $\beta_L'(\equiv\beta_M)$-form the chains are very probably packed predominantly in the orthorhombic manner as is common with many long-chain hydrocarbons and other long-chain crystals.[7] This contrasts with the polymorphism of 1 : 3-diglycerides where both main crystal forms appear to have the hydrocarbon chains packed in the triclinic manner (cf. the single band at 717 cm.$^{-1}$ in the spectrum of 1 : 3 distearin).

I thank the Directors of Unilever Limited for permission to publish this paper.

UNILEVER LIMITED, PORT SUNLIGHT, CHESHIRE. [*Received, June* 3*rd*, 1958.]

[6] Lutton, *J. Amer. Oil Chemists' Assoc.*, 1950, **27**, 276.
[7] Chapman, *J.*, 1957, 4489.

XUM

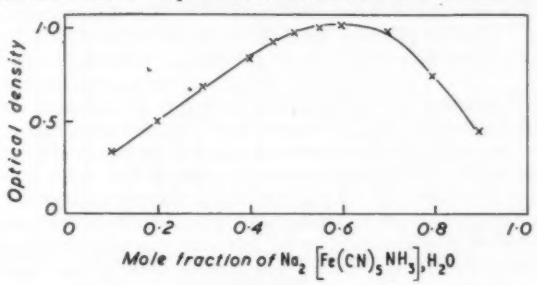
943. *Reactions of Disodium Pentacyanoamminoferrate with Aromatic Amines. Part II.*[1] *The Preparation and Properties of Compounds containing the Pentacyano-(p-anilinoanilino)ferrate Ion.*

By E. F. G. Herington.

The reaction of the salt $Na_2[Fe(CN)_5NH_3]$ with aniline in alkaline solution is shown to give rise to the compound $Na_3[Fe(CN)_5{\cdot}NH{\cdot}C_6H_4{\cdot}NHPh]$, identical with the complex produced by the reaction of the same salt with *p*-aminodiphenylamine. Reduction of the complex ion prepared from aniline yields *p*-aminodiphenylamine, and reaction of the complex with nitrous acid gives the diazo-compound derived from *p*-aminodiphenylamine. The deep blue-green aqueous solution of the complex exhibits an absorption maximum at 660 mμ ($\log_{10}\varepsilon$ 4·1). Some of the heavy-metal salts of the pentacyano-*p*-anilinoanilinoferrate ion are precipitated from dilute acid solution as intensely coloured solids. Paper electrophoresis of aqueous solutions of the complex which had been stored for several months indicated that it decomposed slowly.

DISODIUM PENTACYANOAMMINOFERRATE,[1,2] $Na_2[Fe(CN)_5NH_3]$, with aniline in alkaline solution gives blue-green solutions but the reaction is more complicated than that between the same reagent and *p*-aminophenol.[1] The salts $Na_2[Fe(CN)_5NH_3]$ and $Na_2[Fe(CN)_5H_2O]$

FIG. 1. *"Continuous variation" experiment to determine the ratio in which the materials react.*



yield the same products with aniline, showing that the ammonia molecule is not involved in the reaction. Paper electrophoresis of the material obtained by the reaction of aniline and disodium pentacyanoamminoferrate indicated the presence of four components. The material in the main band formed a blue-green zinc salt, which, after purification, was shown to have a composition $Zn_3[Fe(CN)_5C_{12}H_{11}N_2]_2,8H_2O$. The molecular ratio in which the reagents were used in the reaction was found by the method of "continuous variation" (Job[3]) employing solutions buffered with borax; it was 3 : 2 for the ratio $Na_2[Fe(CN)_5NH_3]$: NH_2Ph (see Fig. 1). The fall in the pH of the solution when the reactants are mixed is ascribed to the following reactions:

$$Na_2[Fe(CN)_5NH_3] + NH_2Ph \rightleftharpoons Na_2[Fe(CN)_5H_2NPh] + NH_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1a)$$

$$Na_2[Fe(CN)_5{\cdot}H_2NPh] + NaOH \rightleftharpoons Na_3[Fe(CN)_5{\cdot}HNPh] + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1b)$$

The small initial rise in the pH (see Experimental section) is the result of reaction (1*a*), but reaction (1*b*) quickly produces a fall. Equations (1*a* and *b*) do not, however, explain the stoicheiometry of the reaction, nor do they account for the simultaneous formation of the salt $Na_3[Fe(CN)_5NH_3]$, so that these reactions must be followed by others.

Reduction of the blue-green ion with sodium dithionite yielded *p*-aminodiphenylamine.

[1] Part I, Herington, *J.*, 1956, 2747.
[2] Herington, *Nature*, 1955, **176**, 80.
[3] Job, *Ann. Chim.* (*France*), 1928, **9**, 113; 1936, **6**, 97.

The complex was also destroyed by reaction with nitrous acid, and the resulting organic compound was coupled with β-naphthol to yield an azo-dye identical (as established by infrared spectroscopy) with that prepared by the diazotisation of *p*-aminodiphenylamine and coupling of the resulting diazo-compound with β-naphthol. Measurement of colour intensities of the respective azo-dyes indicated that the conversion of aniline into *p*-aminodiphenylamine by $Na_3[Fe(CN)_5NH_3]$ was almost quantitative. These observations demonstrate that the blue-green ion has the formula $[Fe(CN)_5{\cdot}HN{\cdot}C_6H_4{\cdot}NHPh]^{3-}$. The structure was confirmed by infrared spectrometry and by paper electrophoresis which showed that the ion obtained by reaction of aniline with disodium pentacyanoamminoferrate was identical with that obtained by reaction of *p*-aminodiphenylamine with the same salt, *i.e.*, by the reaction:

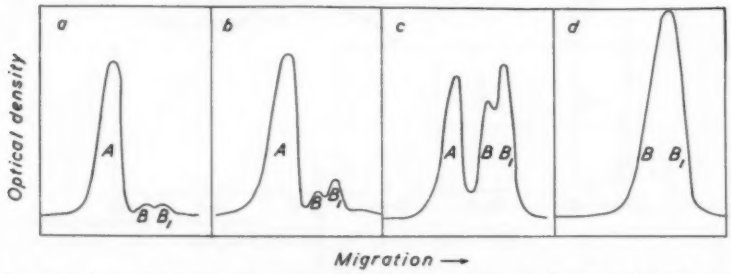
$$Na_3[Fe(CN)_5NH_3] + H_2N{\cdot}C_6H_4{\cdot}NHPh + NaOH = Na_3[Fe(CN)_5{\cdot}HN{\cdot}C_6H_4{\cdot}NHPh] + H_2O + NH_3 \quad . \quad (2)$$

Therefore the reaction between aniline and disodium pentacyanoamminoferrate can be represented by equation (3):

$$3Na_3[Fe(CN)_5NH_3] + 2NH_2Ph + 3NaOH = Na_3[Fe(CN)_5{\cdot}HN{\cdot}C_6H_4{\cdot}NHPh] + 2Na_3[Fe(CN)_5NH_3] + NH_3 + 3H_2O \quad . \quad (3)$$

in agreement with the observed stoicheiometry, the pH change, the simultaneous formation of the salt $Na_3[Fe(CN)_5NH_3]$, the analysis of the zinc salt, with the material produced by reduction and with the compound formed by the reaction with nitrous acid.

FIG. 2. *Paper electrophoresis.*



a) 1 *day*, (*b*) 3 *days*, (*c*) 15 *days*, (*d*) 71 *days after mixing aniline and* $Na_3[Fe(CN)_5NH_3]$ *solutions. A is a blue-green band, B and* B_1 *are violet-blue bands.*

Some of the properties of the complex ion can be explained readily in terms of a canonical form in which the iron is bivalent and the nitrogen carries an odd electron. Thus, for example, the frequency and intensity of the cyano-bands in the infrared spectrum resemble those of zinc ferrocyanide. However the lead salt, unlike lead ferrocyanide, is soluble in dilute acetic acid.

Clearly the reactions of *p*-aminophenol and of aniline with $Na_3[Fe(CN)_5NH_3]$ differ in that the hydroxyl group in *p*-aminophenol stabilises the ion $[Fe(CN)_5{\cdot}NH{\cdot}C_6H_4{\cdot}OH]^{3-}$ (see Part I), whereas the absence of such a hydroxyl group in aniline causes the anilino-group first prduced within the complex to be unstable so that further reactions take place until the relatively stable ion $[Fe(CN)_5{\cdot}HN{\cdot}C_6H_4{\cdot}NHPh]^{3-}$ is formed. This can, however, slowly undergo a change as revealed by paper electrophoresis (see Figs. 2*a*—*d*).

Many of the salts of the pentacyano-(*p*-anilinoanilino)ferrate ion are highly coloured; the sodium salt exhibits maximum absorption at 660 mμ ($\log_{10}\varepsilon$ 4·1). The lead and the uranyl salt are soluble in 0·2N-acetic acid, but several of the heavy metals give insoluble precipitates. The metal salts were investigated by placing a drop of the heavy-metal nitrate or chloride solution on paper which was then sprayed with a solution of sodium pentacyano-(*p*-anilinoanilino)ferrate purified by electrophoresis. The paper was washed

with 0·2N-acetic acid to remove excess of reagent, and the paper was then examined for colour. The result depends both on the insolubility of the salt in 0·2N-acetic acid and on the colour of the salt. The pentacyano-(*p*-anilinoanilino)ferrates of alkali and alkaline-earth metals are soluble in dilute acid. However, the following salts are insoluble: cupric, blue; silver, blue-green; zinc, blue-green; cadmium, blue; mercuric, violet-blue (soon decolorised in air); mercurous, blue; zirconium, green. The aluminium salt is not precipitated. Stannic chloride gives no colour but the stannous salt gives a pale green precipitate which rapidly loses its colour in air. The lead and the thorium salt give no colours. Antimony trichloride does not give a stain but bismuth (Bi^{3+}) gives a green precipitate. Solutions of the rare earths (1 mg. of the oxides of Ce, Pr, Gd, Nd, and Eu, severally, in 1 ml. of solution) did not give stains on the paper. Chromium nitrate produced a faint blue stain but ammonium molydate, sodium tungstate, and uranyl nitrate did not. Manganese (Mn^{2+}) gave a brown spot; iron (Fe^{3+}), cobalt (Co^{2+}), and nickel (Ni^{2+}) gave coloured precipitates which were blue, green, and green respectively.

Experimental

A method for the preparation of disodium pentacyanoamminoferrate has been described.[1] Freshly distilled aniline was used.

p-*Aminodiphenylamine.*—*N*-Nitrosodiphenylamine [4] was isomerised to *p*-nitrosodiphenylamine (Fischer and Hepp [5]). This was reduced to *p*-aminodiphenylamine by tin and hydrochloric acid, as recommended by Ikuta,[6] except that instead of the tin salt being treated with hydrogen sulphide, the base was extracted with ether after the complex had been decomposed with excess of sodium hydroxide. Removal of the ether left the amine, m. p. 64° (from benzene); acetyl compound, m. p. 154°.

Diazotisation and Coupling of p-*Aminodiphenylamine.*—*p*-Aminodiphenylamine (0·25 g.) in acetic acid (5 ml.) and water (60 ml.) at 0° was treated with sodium nitrite (0·5 g.) in cold water (25 ml.). After 5 min. the diazo-compound was extracted with ethyl methyl ketone (100, 25, and 25 ml.); the extract was washed with water and was then added to β-naphthol (0·7 g.) in water (100 ml.) containing sodium hydroxide (5 g.). The resulting azo-dye was extracted with two further quantities of ethyl methyl ketone so that the overall weight of the wet ketonic solution finally obtained was 84 g. A portion of solution was used to measure the amount of *p*-aminodiphenylamine formed from aniline (see below) and another portion was evaporated and the infrared spectra of the resulting purplish-black solid were recorded.

Paper Electrophoresis.—This was carried out as previously described.[1] A solution containing the complex was prepared by shaking aniline (0·18 g.) with $Na_2[Fe(CN)_5NH_3],H_2O$ (0·7 g.) in 0·025N-sodium hydroxide (20 ml.) for 12 hr. The resulting solution was stored at room temperature and samples were withdrawn at appropriate intervals. Electrophoreses of portions of the blue-green solution of the complex (0·025 ml.) were carried out on paper saturated with 0·1N-sodium hydroxide. The current was passed for 3·5 hr. (3·5 v/cm.), then the paper was treated with M-zinc nitrate solution, washed with 2N-acetic acid, and air-dried. The paper was clarified by means of liquid paraffin and the light adsorption was measured by the aid of an E.E.L. scanner fitted with a Chance Green-Glass Filter.

Fig. 2*a* shows the curve obtained from a sample of the complex stored for 1 day. The paper strip exhibited a blue-green band *A*, and two small violet-blue bands *B* and B_1. The bands in Fig. 2*a* had moved from the left under the action of the applied potential. Fig. 2*b*, *c*, and *d*, obtained from samples stored for 3, 15, and 71 days respectively, showed an additional yellow band to the right of B_1 that was probably due to the ion $[Fe(CN)_5NH_3]^{3-}$ since the yellow band gave coloured precipitates with acid solutions of the radicals Zn^{2+}, Fe^{3+}, Fe^{2+}, Pb^{2+}, Cu^{2+}, and UO_2^{2+} similar to those produced by the ion $[Fe(CN)_5NH_3]^{3-}$ with the same radicals.

Figs. 2 show that in 71 days the material responsible for band *A* had disappeared and had been replaced by the materials in bands *B* and B_1.

[4] Hickinbottom, "Reactions of Organic Compounds," Longmans, Green & Co., London, 1941, p. 286.
[5] Fischer and Hepp, *Ber.*, 1886, **19**, 2991.
[6] Ikuta, *Annalen*, 1888, **243**, 272.

XUM

Preparation and Analysis of Zinc Pentacyano-p-(*anilinoanilino*)*ferrate*.—On to aniline (0·16 g.) was poured a solution containing $Na_2[Fe(CN)_5NH_3],H_2O$ (0·7 g.) in 0·1N-sodium hydroxide (5 ml.). The solution was shaken for 30 min., then 2 ml. portions of the solution were put on the upper ends of two Whatman's seed test papers. The papers were inserted into a preparative paper-electrophoresis apparatus of the type described by Cannon and Gilson [7] but fitted with carbon-rod instead of platinum-wire electrodes. The papers were saturated with 0·1N-sodium hydroxide and an electric current was passed. After 3·5 hr. the papers were removed, the blue-green bands cut out, and the materials in them extracted at room temperature with 0·1N-sodium hydroxide. To the resulting coloured solution zinc nitrate (1 g.) in water (5 ml.) was added, and then glacial acetic acid (12 ml.). The blue-green precipitate was removed by means of a centrifuge, and the highly coloured gel was washed with water until the decanted liquid was neutral. The *zinc salt* was dried [NaOH, then $Mg(ClO_4)_2$ in a vacuum] {Found: C, 38·6; H, 3·6; N, 18·2; Zn, 17·9; Fe, 10·7. $Zn_3[Fe(CN)_5HN{\cdot}C_6H_4{\cdot}NH{\cdot}C_6H_5]_2,8H_2O$ requires C, 37·9; H, 3·6; N, 18·2; Zn, 18·2; Fe, 10·4%}.

" Continuous Variation."—This experiment was carried out as described previously.[1] The absorption of each solution was measured with a Spekker absorptiometer employing 1 cm. cells, a tungsten lamp, and filter No. 606. The readings obtained for the solutions 24 hr. after mixing are plotted in Fig. 1, which shows that the maximum colour occurs for a solution containing 0·6 mol. of inorganic salt. This curve has a very flat maximum, showing that the complex obtained from aniline is less stable than that from *p*-aminophenol (compare Fig. 1 of this paper with the Figure in ref. 1). Other curves which were obtained indicated that the colour had not fully developed 2·25 hr. after mixing and that the complex had started to decompose 120 hr. later.

pH *Measurements*.—The measurements were made with an " Alki " glass electrode and a pH-meter (Cambridge Instrument Co.).[1] Aniline (0·02 ml.) was dissolved in distilled water (10 ml.), and the pH was adjusted to 11·16 by addition of 0·02N-sodium hydroxide (0·93 ml.). The salt $Na_2[Fe(CN)_5NH_3],H_2O$ (0·101 g.) was dissolved in water (20 ml.) and the pH similarly adjusted to 11·14. The aniline solution was poured into the salt solution and pH readings were taken. The pH rose to 11·20 after 1 min., fell to 10·85 after 4 min., and then very rapidly to 8·45 after 5 min.; 16 min. later the value was 8·4 and after 60 min. was 8·18. Recalibration of the electrode at the end of the experiment showed that a reading of 9·60 corresponded to a pH of 9·15, *i.e.*, the meter was reading 0·45 unit too high. The overall pH change was thus from 11·14 before the solutions were mixed to 7·73 after 1 hr.

Reduction of the Complex Ion formed by the Reaction of Aniline with $Na_2[Fe(CN)_5NH_3]$.—Reducing agents, such as hydrazine hydrate, sodium dithionite, sodium hydrogen sulphite, hydrogen sulphide, and a hydrochloric acid solution of stannous chloride destroyed the colour and decomposed the complex. Zinc in hydrochloric acid and hydroxylamine hydrate did not.

The following experiment showed that *p*-aminodiphenylamine was liberated when the complex was reduced. The salt $Na_2[Fe(CN)_5NH_3],H_2O$ (2·5 g.), dissolved in 0·02N-sodium hydroxide (10 ml.), was poured on aniline (0·25 ml.). After the mixture had been stirred for 2 hr. a 5% w/w solution of sodium hydroxide (10 ml.) was added and the complex was reduced by the addition of solid sodium dithionite. The solution which changed to a pale-greenish colour and contained a suspended solid was extracted with ether. A brown oil which slowly solidified was obtained after removal of the ether. A portion of this material was chromatographed in benzene on alumina with 0·5% v/v of ethanol in benzene as eluant. A single band moved down but a small amount of dirty brown residue was left at the top of the column, showing that the product recovered from the ether was essentially one component. The infrared spectrum of the material was identical with that of authentic *p*-aminodiphenylamine, and the material yielded an acetyl derivative, m. p. 158°, mixed m. p. 154° with *p*-acetamidodiphenylamine.

Reaction of Nitrous Acid with the Product formed by the Action of $Na_2[Fe(CN)_5NH_3]$ *on Aniline*.—The salt $Na_2[Fe(CN)_5NH_3],H_2O$ (2·5 g.), dissolved in 0·02N-sodium hydroxide (70 ml.), was poured on aniline (0·25 g.). The solution was stirred for 1 hr. and then cooled in ice after acetic acid (5 ml.) had been added. Sodium nitrite (1 g.) in ice-cold water (50 ml.) was added, and after 5 min. the solution was extracted with ethyl methyl ketone (100, 25, and 25 ml.). The extract was washed with water and shaken with an aqueous solution (120 ml.) of β-naphthol (0·7 g.) and sodium hydroxide (5 g.). The resulting red azo-compound was extracted into ethyl methyl ketone (wt. of final extract 101 g.). A portion of this solution was evaporated to dryness

[7] Cannon and Gilson, *Chem. and Ind.*, 1954, **32**, 120.

and the purplish-black solid was shown by means of its infrared spectrum to be the same compound as obtained from the coupling of diazotised *p*-aminodiphenylamine and β-naphthol (see above). By diluting a further portion of the ketonic solution (0·2 ml.) with ethyl methyl ketone (9·8 ml.) and measuring the light absorption in a 1 cm. cell with filter No. 603 in a Spekker absorptiometer it was shown that approximately 100% of the aniline had been converted into *p*-aminodiphenylamine; the azo-compound prepared from authentic *p*-aminodiphenylamine was used as a standard for the measurements.

Reactions of p-*Aminodiphenylamine with* $Na_2[Fe(CN)_5NH_3]$.—*p*-Aminodiphenylamine (0·36 g.) was shaken for 17 hr. with $Na_3[Fe(CN)_5NH_3],H_2O$ (0·7 g.) in 0·025N-sodium hydroxide (20 ml.). The blue-green solution was filtered and examined by paper electrophoresis. The appearance of the paper was similar to that produced by a freshly prepared sample of the aniline complex (see Fig. 2*a*) except that band *B* was slightly weaker. Paper electrophoresis with a 1 : 1 mixture by volume of the aniline product and of the *p*-aminodiphenylamine product showed that the corresponding coloured bands had the same mobility. Moreover, paper electrophoresis of a sample of the *p*-aminodiphenylamine product which had been kept for 14 days showed that this material decomposed in the same way as the complex prepared from aniline. The complex freshly prepared from *p*-aminodiphenylamine and the salt $Na_2[Fe(CN)_5NH_3]$ was reduced with sodium dithionite and the liberated base extracted with benzene. The material recovered was shown to be *p*-aminodiphenylamine by its m. p. and mixed m. p. 64°.

Zinc Salt of the Complex prepared by Reaction of p-*Aminodiphenylamine with* $Na_2[Fe(CN)_5NH_3]$.—The salt $Na_3[Fe(CN)_5NH_3],H_2O$ (0·35 g.) in 0·025N-sodium hydroxide (10 ml.) was poured on *p*-aminodiphenylamine (0·18 g.) and was shaken for 20 hr. The solution was filtered and diluted to 200 ml., and acetic acid (20 ml.) was added, followed by 0·1M-zinc nitrate (35 ml.). The precipitate was filtered off, washed until neutral, and dried [NaOH and then $Mg(ClO_4)_2$ in a vacuum]. The infrared spectrum obtained from this material dispersed in a potassium chloride disc was identical with that from a purified sample of the zinc salt made from aniline and $Na_2[Fe(CN)_5NH_3]$ (see below).

Infrared Spectrum of Zinc Pentacyano-(p-*anilinoaniline)ferrate.*—The spectrum of the zinc salt, prepared from aniline and $Na_2[Fe(CN)_5NH_3]$ purified by paper electrophoresis (see above) was obtained by incorporating the solid in a pressed potassium chloride disc. The Table shows the spectrum of this material and of some related compounds.

The bands at 2093 cm.$^{-1}$ due to the CN group in zinc pentacyano-(*p*-anilinoanilino)ferrate resembled the band produced by CN groups in zinc ferrocyanide both in frequency and in width.

Infrared absorption bands (cm.$^{-1}$).

Zn ferricyanide.....	3450 sb; 2177 s.
Zn ferrocyanide	3350 sb; 2110 s.
Zn pentacyano-(*p*-anilinoanilino)ferrate	3440 m; 3305 m; 2093 s; 1611 m; 1587 m.sh.; 1567 m.sh; 1490 m; 1427 m; 1393 m; 1178 m; 1026 w; 1000 w; 867 w; 853 w; 798 w; 754 w; 695 w.
Aniline (liquid)	4950 w; 4460 w; 3990 w; 3330 s; 3210 sh; 3020 m; 2745 w; 2620 w; 2330 w; 2145 w; 2085 w; 1928 w; 1838 w; 1776 w; 1692 sh; 1620 s; 1602 s; 1502 s; 1470 sh; 1385 w; 1333 w; 1316 w; 1280 s; 1200 w; 1176 m; 1155 m; 1120 w; 1053 w; 1030 w; 998 w; 883 m; 828 m; 755 s; 693 s.
p-Aminodiphenylamine (solid as thin film)	3400 s; 3070 m; 2905 w; 1626 sh; 1600 s; 1518 s; 1502 sh; 1453 w; 1413 w; 1387 w; 1330 sh; 1305 s; 1266 s; 1244 sh; 1221 sh; 1175 m; 1152 w; 1114 w; 1078 w; 1026 w; 1011 w; 993 w; 875 m; 825 sh; 792 w; 747 s; 693 s.

b = broad, m = medium, s = strong, sh = shoulder, w = weak.

Moreover, the optical density of the disc (0·375″ diam.) containing 1 mg. of the complex salt was 1·58, similar to that for a disc containing zinc ferrocyanide rather than (0·73) for one containing zinc ferricyanide.[2,8] The spectrum of zinc pentacyano-(*p*-anilinoanilino)ferrate does not resemble closely that of either aniline or *p*-aminodiphenylamine but has many bands attributable

[8] Herington and Kynaston, *J.*, 1955, 3555.

XUM

to the organic part of the ion. The band at 754 cm.$^{-1}$ probably arises from the out-of-plane CH bending absorption in the aromatic ring.[9]

A preliminary note on this work has been published.[2] I thank Mr. W. Kynaston for the infrared measurements. The work described formed part of the research programme of the Chemical Research Laboratory and this paper is published by permission of the Director, National Chemical Laboratory, Teddington, Middlesex.

National Chemical Laboratory,
Teddington, Middlesex. [*Received, June 6th,* 1958.]

[9] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 65.

---

944. *Hydroaromatic Steroid Hormones. Part VI.* Some D-Homo-analogues Lacking Ring* B.

By A. J. Birch, E. Pride, and Herchel Smith.

The preparation of 9-methyl-6-(4-oxo*cyclo*hex-1-enyl)-*trans*-decal-1β-ol (VIII) † and **1α-ethyn**yl-9-methyl-6-(4-oxo*cyclo*hex-1-enyl)-*trans*-decal-1β-ol (IX) (steroid αβ convention) in admixture with the respective αβ-unsaturated ketones is described. Addition of ethylmagnesium bromide to a 9-methyl-*trans*-decal-1-one gives a mixture containing a 1α-ethyl-9-methyl-*trans*-decal-1β-ol.

Our previous work on relationships between structure and biological activity in non-œstrogenic steroid hormones has been concerned chiefly with (*a*) omission of the 19-methyl group and (*b*) omission of the 19- and 18-methyl groups with ring D six-membered. Clinically useful compounds have emerged.[1] Recent work has shown that anabolic activity and progestational activity are structurally less specific than was previously supposed; for example 19-nor-14β : 17α-progesterone[2] and 8α-progesterone[3] retain biological activity. We consequently deemed worthwhile the synthesis of some compounds containing incomplete ring-systems.

An obvious substance for study is the (±)-form of the ketone (I) which is an analogue of testosterone. After completion of our work the synthesis of this substance in admixture with the βγ-unsaturated isomer was reported.[4] The route employed, although similar to that described below, was rather more complex. The starting material for the present synthesis is the hydroxy-ketone (II), now more conveniently available [5] than previously.[6] In order to form rings C and D of a testosterone analogue the 1-hydroxyl group (analogous to 17α in D-homosteroids) must be *cis* to the angular methyl group. This would be expected from the method of production, but we have obtained confirmatory evidence. The ketol (II) was reduced with lithium in liquid ammonia to the saturated compound (III) which is a *trans*-decalol because it differs from the *cis*-isomer prepared earlier and converted into a known 9-methyl-*cis*-decal-1-ol.[7] The ketol (III) was oxidised with chromium trioxide in acetone to the dione (IV) which with lithium and ethanol in liquid ammonia yielded a diol (V) identical with that formed by direct reduction of the ketol (II) with the same reagent. Consequently the 1-hydroxyl group in (II) almost certainly has the

* Part V, Birch and Smith, *J.*, 1956, 4909.

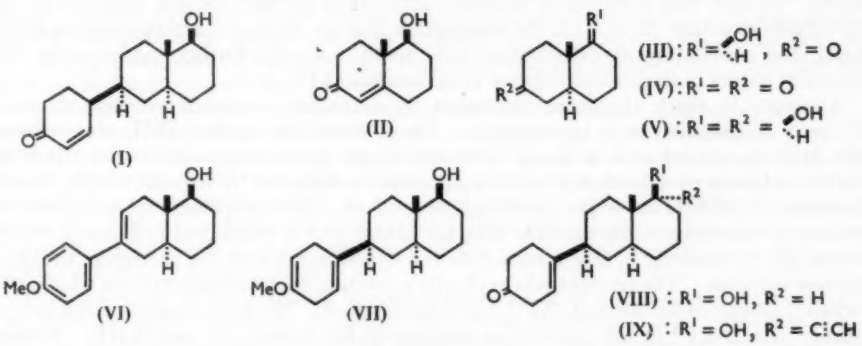
† All the substances prepared were racemic compounds, of which the formulæ represent only one form.

[1] Cf. Part V and references cited therein.
[2] Barber and Ehrenstein, *Annalen*, 1957, **603**, 89.
[3] Djerassi, Manson, and Segaloff, *J. Org. Chem.*, 1956, **21**, 490.
[4] Jaeger, *Tetrahedron*, 1958, **2**, 326.
[5] Cocker and Halsall, *J.*, 1957, 3441.
[6] Birch, Quartey, and Smith, *J.*, 1952, 327.
[7] Jaeger, Robinson, and Smith, unpublished work.

stable equatorial configuration, *cis* to the 9-methyl group. This is supported by the presence of a single band at 1240 cm.$^{-1}$ in the infrared spectrum of the acetate of the ketol (III). An axial acetoxy-compound by analogy with axial 2-, 3-, and 4-acetoxy-5α-steroids would be expected to show a complex band in the same region.[8]

The heterogeneous reaction of the ketol (III) with *p*-methoxyphenylmagnesium bromide in ether or tetrahydrofuran gave, after treatment of the product with mineral acid, the substance (VI) in yields varying from 40 to 60%. Improved and consistent yields of this compound were obtained from the homogeneous reaction of *p*-methoxyphenyl-lithium and the ketol in tetrahydrofuran. The double bond should be more stable in the 6 : 7- than in the 5 : 6-position, and the substance (VI) is formulated on this basis. Attempts to reduce the double bond with lithium in liquid ammonia or by catalytic methods were unsuccessful. Reduction of this compound (VI) with lithium and ethanol in liquid ammonia gave a decalol in which a dihydrobenzene substituent is probably attached equatorially as in formula (VII). Hydrolysis with oxalic acid then gave the ketone (VIII), converted by hot mineral acid into an equilibrium mixture of the isomers (I) and (VIII) containing, as with other 4-alkyl*cyclo*hex-2-enones,[10] an appreciable quantity (estimated as 30%) of the βγ-unsaturated ketone.

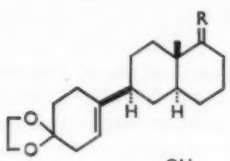
During this work it was reported that 17α-ethynyl-17-hydroxyœstr-5(10)-en-3-one shows promise in controlling menstrual disorders and as a physiological contraceptive.[11] The analogue (IX) was therefore required. The ketal (X) [from the ketone (VIII)] with chromium trioxide in pyridine gave the decalone (XI) which with lithium acetylide in



refluxing tetrahydrofuran afforded the alcohol (XII). Subsequent acid hydrolysis furnished an equilibrium mixture of the βγ- and the αβ-unsatuated ketone (IX and isomer). Attempts to avoid the equilibration step by using the decalol (VII) as starting material were unsuccessful because of the failure to oxidise selectively the alcoholic to a ketonic group: Oppenauer oxidation in toluene was unsuccessful and the chromium trioxide–pyridine complex gave the ketone (XIII). The hydroxyl group in the alcohol (IX) is assigned the β-configuration by analogy with the known mode of addition of alkali-metal acetylides to 17-oxo-steroids.[12] However, it seems relevant that whereas methylmagnesium bromide with 17-oxo-steroids gives 17α-methyl-17β-alcohols, with D-homo-17a-oxo-steroids the 17aβ-methyl-17aα-ols are formed.[13] Accordingly we have sought evidence on

[8] Cf. Braude and Waight in Klyne's "Progress in Stereochemistry," Butterworths, London, 1954, Vol. I, p. 126.
[9] Turner, Meador, and Winkler, *J. Amer. Chem. Soc.*, 1957, **79**, 4112 and references cited therein.
[10] Cf., *e.g.*, Birch and Mukherji, *J.*, 1949, 2531.
[11] *Chem. Eng. News.*, 1957, **35**, No. 23, p. 30.
[12] Cf. Reichstein and Meystre, *Helv. Chim. Acta*, 1939, **22**, 728; Reichstein and Gatzi, *ibid.*, 1938, **21**, 1185.
[13] Heusser, Wahba, and Winternitz, *ibid.*, 1954, **37**, 1052.

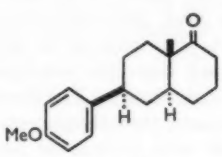
this point. Hydrogenation of the ketal (XII) gave the alcohol (XIV) in which the hydroxyl group is probably equatorial because of its resistance to dehydration by phosphorus oxychloride in pyridine, iodine in refluxing benzene, or refluxing acetic anhydride. 17β-Hydroxy-17α-alkyl-steroids and their D-ring homologues behave similarly.[13] The alcohol



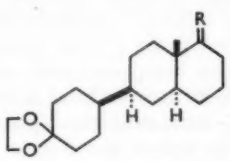
(X) : R = OH, H

(XI) : R = O

(XII) : R = OH, C≡CH



(XIII)



(XIV) : R = OH, Et

(XV) : R = Et, OH

(XVI) : R = O

(XIV) was dehydrated in refluxing benzene in the presence of toluene-*p*-sulphonic acid. It was hoped that oxidation of the resulting olefin with perbenzoic acid would yield, by preferential attack at the side of the molecule remote from the 9-methyl group, an epoxide which on diaxial ring opening with lithium aluminium hydride would give an axial decalol. In fact, this sequence of reactions afforded an alcohol isomeric with (XIV) and of probable structure (XV). On the assumption that no skeletal rearrangement occurred during the acid-catalysed dehydration this result provides further evidence for the equatorial nature of the hydroxyl group in the alcohol (XIV).

Attempts to reach the same conclusion by a reaction sequence avoiding an acid-catalysed dehydration were unsuccessful. Thus, whilst the alcohol (XII) was reduced with lithium and ethanol in liquid ammonia to an olefin which should be either an ethylidenedecalin or a 1-ethyl-Δ^1-octalin, epoxidation followed by reduction with lithium aluminium hydride failed to give a crystalline product. For comparison we examined the reaction of ethylmagnesium bromide with the ketone (XVI) which was prepared from the alcohol (X) by catalytic hydrogenation followed by oxidation with the chromium trioxide–pyridine complex. The product was evidently a mixture of stereoisomers from which only a small quantity of the alcohol (XIV) could be obtained. We have confirmed the lack of androgenic activity [4] in the equilibrium mixture of the ketones (I) and (VIII). Results of other biological tests will be reported later.

Experimental

M. p.s were determined on a Kofler block. Ultraviolet-light absorption data refer to ethanol solutions. Infrared spectra were determined for carbon disulphide solutions unless otherwise stated. Light petroleum means the fraction of b. p. 60—80°. Florisil is a grade of Florida fuller's earth supplied by the Floridin Co., Warren, Pennsylvania.

5β-*Hydroxy*-10β-*methyl*-trans-*decal*-2-*one* (III).—5β-Hydroxy-10β-methyl-$\Delta^{1(9)}$-octal-2-one (5 g.) in tetrahydrofuran (100 c.c.) was added to lithium (0·58 g.) in liquid ammonia (250 c.c.; distilled from sodium). After 1·5 hours' stirring, sodium nitrite was added to discharge the blue colour and the ammonia was allowed to evaporate. Water (200 c.c.) was added and the product collected with ether. The gum in benzene (10 c.c.) was adsorbed on Florisil (50 g.). Elution with benzene (1 l.) gave β-*hydroxy*-10β-*methyl*-trans-*decal*-2-*one* (2·86 g.), m. p. 68—70° (from ether at −15°) (Found: C, 72·3; H, 9·85. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·95%), $\nu_{max.}$ 3635 and 1711 cm.$^{-1}$.

The *acetate* (from ether), after distillation at 75°/0·05 mm., had m. p. 49—50° (Found: C, 69·8; H, 8·9. $C_{13}H_{20}O_3$ requires C, 69·6; H, 9·0%), $\nu_{max.}$ 1740, 1710, 1240, 1030, and 1010 cm.$^{-1}$.

9β-*Methyl*-trans-*decalin*-1 : 6-*dione* (IV).—Chromium trioxide (2·67 g.) in 8·45N-sulphuric acid (1 c.c.) was added to the ketol (III) in acetone (25 c.c.). After 2 min. the green solution was poured into water (100 c.c.), and the crystalline product was collected with ether. Distillation twice at 90°/0·03 mm. gave the 9β-*methyl*-trans-*decalin*-1 : 6-*dione*, m. p. 53—55° (Found: C, 73·2; H, 9·1. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·95%), $\nu_{max.}$ 1705 and 1715 cm.$^{-1}$.

Reduction of the dione (20 mg.) with lithium (50 mg.) and ethanol (0·8 g.) in liquid ammonia (50 c.c.) and tetrahydrofuran (5 c.c.) gave the diol (V), m. p. 125—132° undepressed by the sample prepared as below and possessing an identical infrared spectrum.

9β-*Methyl*-trans-*decalin*-1β : 6β-*diol* (V).—Lithium (0·1 g.) was added to 5β-hydroxy-10β-methyl-$\Delta^{1(9)}$-octal-2-one (0·5 g.) in tetrahydrofuran (12 c.c.)–liquid ammonia (50 c.c.), and the whole was stirred for 15 min. Ethanol (1 c.c.) was rapidly run in to discharge the blue colour. After evaporation of the ammonia, water (50 c.c.) was added and the product isolated with ether. The gum was adsorbed from chloroform–ethanol (100 : 1; 5 c.c.) on Florisil. Elution with the same solvent (100 c.c.) gave 9β-*methyl*-trans-*decalin*-1β : 6β-*diol* (200 mg.), m. p. 132—133° (from ether) (Found: C, 71·4; H, 11·0. $C_{11}H_{20}O_2$ requires C, 71·7; H, 10·9%).

6-p-*Methoxyphenyl*-9β-*methyl*-trans-Δ^6-*octalin*-1β-*ol* (VI).—(*a*) 5β-Hydroxy-10β-methyl-*trans*-decal-2-one (1·5 g.) in ether (45 c.c.) was added with stirring to *p*-methoxyphenyl-lithium [from butyl-lithium (2·03 g.) and *p*-bromoanisole (6·6 g.)] in ether (100 c.c.) at −30° under nitrogen. Tetrahydrofuran was added to dissolve the precipitate, and the solution was stirred at −15° for 30 min., warmed to 0° during 15 min., and poured on ice. The product was isolated with ether and heated at 100°/0·1 mm. to remove anisole and *p*-bromoanisole. The gum was refluxed for 30 min. in benzene (100 c.c.) containing a crystal of iodine (Dean–Stark water-separator). The cooled solution was washed with aqueous sodium hydrogen sulphite, dried ($MgSO_4$), and evaporated. The residue was adsorbed from benzene (20 c.c.) on Florisil (50 g.). Elution with benzene and crystallisation of the solid from benzene gave 6-p-*methoxyphenyl*-9β-*methyl*-trans-Δ^6-*octalin*-1β-*ol* (1·68 g., 74%), m. p. 113—115° (Found: C, 79·1; H, 9·1. $C_{18}H_{24}O_2$ requires C, 79·4; H, 8·9%), $\nu_{max.}$ 3615, 802, and 837 cm.$^{-1}$, $\lambda_{max.}$ 255, 256, and 258 mμ (ε 10,100, 10,100, and 9900 respectively).

(*b*) The ketol (III) (1 g.) in tetrahydrofuran (100 c.c.) was added to a boiling solution of *p*-methoxyphenylmagnesium bromide (from the metal, 0·526 g.) in tetrahydrofuran (120 c.c.) under nitrogen. The suspension was refluxed for 1·5 hr., and on cooling was poured into ice-cold 4N-sulphuric acid (500 c.c.). After 30 min. the product was extracted with ether. It was adsorbed from the saturated solution in benzene on Florisil. Elution with light petroleum–benzene (9 : 1) gave 4 : 4′-dimethoxydiphenyl, m. p. 173—175°, and elution with light petroleum benzene (1 : 1) and benzene gave (from benzene) the octalin (VI) (0·61 g.), m. p. 113—115°, identical with that prepared as in (*a*).

6β-(2 : 5-*Dihydro*-4-*methoxyphenyl*)-9β-*methyl*-trans-*decal*-1β-*ol* (VII).—The octalinol (VI) (2 g.) in tetrahydrofuran (100 c.c.) was added with stirring to lithium (1·5 g.) in liquid ammonia (400 c.c.). After 5 min. ethanol was added during 10 min. After discharge of the blue colour, water (200 c.c.) was added and the product collected with ether. Crystallisation of the gum from ether–light petroleum gave 6β-(2 : 5-*dihydro*-4-*methoxyphenyl*)-9β-*methyl*-trans-*decal*-1β-*ol* (1·18 g.), m. p. 100—110°, raised to 111—113° by recrystallisation from di*iso*propyl ether (Found: C, 77·95; H, 10·4. $C_{18}H_{28}O_2$ requires C, 78·2; H, 10·2%), $\nu_{max.}$ 3620, 1660, and 1690 cm.$^{-1}$.

6β-(4-*Oxo*cyclo*hex*-1-*enyl*)-9β-*methyl*-trans-*decal*-1β-*ol* (VIII).—Oxalic acid dihydrate (0·375 g.) in water (5 c.c.) was added to the decalol (VII) in methanol (25 c.c.) and the cloudy solution kept at 25° for 40 min. Saturated aqueous sodium hydrogen carbonate was added and the product was extracted with ether. The gum was distilled at 200° (bath-temp.)/0·02 mm. to give 6β-(4-*oxo*cyclo*hex*-1-*enyl*)-9β-*methyl*-trans-*decal*-1β-*ol* (236 mg.) (Found: C, 77·5; H, 10·2. $C_{17}H_{26}O_2$ requires C, 77·8; H, 10·0%), $\nu_{max.}$ 3620 and 1725 cm.$^{-1}$.

The 2 : 4-*dinitrophenylhydrazone* (from ethanol) had m. p. 100—110° (Found: C, 62·3; H, 7·0. $C_{23}H_{30}O_5N_4$ requires C, 62·5; H, 6·9%), $\lambda_{max.}$ 228, 229, and 360 mμ (ε 17,700, 17,700, and 23,500 respectively).

The foregoing decalol was refluxed in ethanol (5 c.c.) containing 2N-hydrochloric acid (2 c.c.) for 5 min., the solution added to saturated aqueous sodium hydrogen carbonate, and the product collected in ether. The infrared spectrum of the gum, which is probably a mixture of the ketones (I) and (VIII), showed bands at 3620, 1718 (strong), and 1680 cm.$^{-1}$ (medium).

6β-(4 : 4-*Ethylenedioxy*cyclo*hex*-1-*enyl*)-9β-*methyl*-trans-*decal*-1β-*ol* (X).—The ketol (VIII)

(1·83 g.) was refluxed for 12 hr. in benzene containing ethylene glycol (6 c.c.) and toluene-*p*-sulphonic acid (*ca.* 40 mg.) (Dean–Stark head). The cooled solution was poured into saturated aqueous potassium hydrogen carbonate (100 c.c.), and the product was extracted with ether. The gum was adsorbed from benzene (20 c.c.) on Florisil (150 g.). Benzene (1·1 l.) eluted a gum which was distilled, to give 6β-(4 : 4-*ethylenedioxy*cyclo*hex*-1-*enyl*)-9β-*methyl*-trans-*decal*-1β-*ol* as a gum, b. p. 200° (bath temp.)/0·2 mm. (Found: C, 74·75; H, 10·1. $C_{19}H_{30}O_3$ requires C, 74·75; H, 9·85%), $\nu_{max.}$ 3620, 1115, 1060, 1025, and 860 cm.$^{-1}$.

6β-(4 : 4-*Ethylenedioxy*cyclo*hex*-1-*enyl*)-9β-*methyl*-trans-*decal*-1-*one* (XI).—The decalol (X) (2 g.) in pyridine (20 c.c.) was added to chromium trioxide (2 g.) in pyridine (20 c.c.). After 20 hr. at room temperature the mixture was poured into 5% aqueous sodium hydroxide (1 l.) and extracted with ether (4 × 200 c.c.). The product was adsorbed from light petroleum (50 c.c.) on Florisil (200 g.), and the column was washed with light petroleum (1 l.). Elution with light petroleum–benzene (1 : 1; 1 l.), benzene (4 l.), and benzene–ether (100 : 1; 2 l.) gave fractions which were combined and distilled, to give 6β-(4 : 4-*ethylenedioxy*cyclo*hex*-1-*enyl*)-9β-*methyl*-trans-*decal*-1-*one* as a gum, b. p. 200° (bath-temp.)/0·5 mm. (Found: C, 75·2; H, 9·5. $C_{19}H_{28}O_3$ requires C, 74·95; H, 9·25%), $\nu_{max.}$ (liquid film) 1700, 1115, 1060, 1020, and 865 cm.$^{-1}$.

6β-(4-*Methoxyphenyl*)-9β-*methyl*-trans-*decal*-1-*one* (XIII).—The decalol (VII) (120 mg.) in pyridine (1 c.c.) was added to chromium trioxide (0·4 g.) in pyridine (4 c.c.). Next day the mixture was poured into water (100 c.c.), and the product collected with ether. Recrystallisation from di*iso*propyl ether–light petroleum gave 6β-(4-*methoxyphenyl*)-9β-*methyl*-trans-*decal*-1-*one* (100 mg.), m. p. 73—75° (Found: C, 79·05; H, 9·0. $C_{18}H_{24}O_2$ requires C, 79·35; H, 8·9%), $\nu_{max.}$ 1710 and 830 cm.$^{-1}$, $\lambda_{max.}$ 223, 224, 276, and 283 mμ (ε 11,800, 11,800, 2500, and 1900 respectively).

1α-*Ethynyl*-6β-(4 : 4-*ethylenedioxy*cyclo*hex*-1-*enyl*)-9β-*methyl*-trans-*decal*-1β-*ol* (XII).—The decalone (XI) (1·5 g.) was stirred with a suspension of lithium acetylide (from the metal, 6 g.) in tetrahydrofuran (150 c.c.) in a stream of acetylene. After 1 hr. the acetylene was replaced by nitrogen. The mixture was stirred overnight at room temperature, refluxed for 1·5 hr., and cooled in ice, then ice-water (500 c.c.) was cautiously added. The product was collected with ether. The gummy crystals were adsorbed from benzene (20 c.c.) on alumina (150 g.). Elution with benzene–ether (5 : 1, 4 l.; 1 : 1, 1 l.) gave (from light petroleum–ether) 1α-*ethynyl*-6β-(4 : 4-*ethylenedioxy*cyclo*hex*-1-*enyl*)-9β-*methyl*-trans-*decal*-1β-*ol* (1·04 g.), m. p. 140—142°, raised to 143—144° by sublimation at 120°/0·03 mm. (Found: C, 76·1; H, 9·2. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·15%), $\nu_{max.}$ (Nujol mull) 3400, 3220, 2110, 1115, 1060, 1020, and 865 cm.$^{-1}$.

1α-*Ethyl*-6β-(4 : 4-*ethylenedioxy*cyclo*hexyl*)-9β-*methyl*-trans-*decal*-1β-*ol* (XIV).—(*a*) The alcohol (XII) (50 mg.) in ethyl acetate (20 c.c.) was shaken with hydrogen over platinum (from platinum dioxide monohydrate, 50 mg.) for 8 hr. The infrared absorption spectrum of the crystalline product showed no band in the 860—870 cm.$^{-1}$ region. It was adsorbed from light petroleum on Florisil (5 g.). Elution with light petroleum–benzene (1 : 1) gave (from light petroleum) 1α-*ethyl*-6β-(4 : 4-*ethylenedioxy*cyclo*hexyl*)-9β-*methyl*-trans-*decal*-1β-*ol* (40 mg.), m. p. 114—116° (Found: C, 75·1; H, 10·7. $C_{21}H_{36}O_3$ requires C, 74·95; H, 10·8%). (*b*) The alcohol (XI) (100 mg.) in ethyl acetate (20 c.c.) was shaken in hydrogen with finely divided platinum (from the dioxide hydrate, 50 mg.) for 12 hr. The product, unlike all compounds in this series which contain a 4 : 4-ethylenedioxy*cyclo*hex-1-enyl residue, showed no band in the infrared 860—870 cm.$^{-1}$ region. It was dissolved in pyridine (1 c.c.) and added to chromium trioxide in pyridine (3 c.c.). After two days the product was obtained in the usual manner and adsorbed from light petroleum on Florisil (5 g.). Elution with benzene gave a ketonic gum (infrared band at 1705 cm.$^{-1}$; no band in 3300—3400 cm.$^{-1}$ region) which was treated with ethylmagnesium bromide in tetrahydrofuran solution in the standard fashion. The resulting gum (infrared band at 3450 cm.$^{-1}$) was chromatographed on Florisil in ether, to give the alcohol (XIV) (2 mg.), m. p. 113—115° undepressed with the material obtained as under (*a*), as the only recognisable product.

1β-*Ethyl*-6β-(4 : 4-*ethylenedioxy*cyclo*hexyl*)-9β-*methyl*-trans-*decal*-1α-*ol* (XV).—The decalol (XII) (45 mg.) was refluxed for 12 hr. in benzene (50 c.c.) containing ethylene glycol (1 c.c.) and toluene-*p*-sulphonic acid (20 mg.) (Dean–Stark water-separator). The cooled solution was poured into sodium hydrogen carbonate solution, and the product was collected with ether and adsorbed from light petroleum on activated alumina. Elution with light petroleum–benzene (9 : 1) gave a gum (40 mg.), the infrared absorption spectrum of which showed a band at 830 cm.$^{-1}$ but no band in the 3600 cm.$^{-1}$ region. The gum was treated with perbenzoic acid

(44 mg.) in chloroform (5 c.c.) at 0°. After 1 hr. ether was added and the solution was washed successively with aqueous ferrous sulphate, water, aqueous sodium hydrogen carbonate, and water and dried ($MgSO_4$). The product was adsorbed from light petroleum on alumina (5 g.). Elution with light petroleum–benzene (9 : 1) gave a gum (36 mg.) which was dissolved in tetrahydrofuran (5 c.c.) and treated with lithium aluminium hydride (200 mg.). After 1 hr. at room temperature the mixture was heated at 50° for 45 min. The product, isolated in the known manner, was adsorbed from light petroleum on Florisil. Elution with light petroleum–benzene (4 : 1) yielded a crystalline fraction which after crystallisation from light petroleum gave 1-β-*ethyl*-6β-(4 : 4-*ethylenedioxy*cyclo*hexyl*)-9β-*methyl*-trans-*decal*-1β-*ol* (34 mg.), m. p. 140—143°, depressed to 80—135° on admixture with the foregoing 1β-alcohol (XII) (Found: C, 74·8; H, 10·5. $C_{21}H_{36}O_3$ requires C, 74·95; H, 10·8%). The infrared absorption spectra of the alcohols (XIV) and (XV) were different.

We thank the Department of Scientific and Industrial Research for a maintenance grant (to E. P.) and Dr. L. Golberg (Benger's Limited, Holmes Chapel, Cheshire) through whose courtesy the biological tests were performed.

THE UNIVERSITY, MANCHESTER, 13. [*Received, July 14th*, 1958.

---

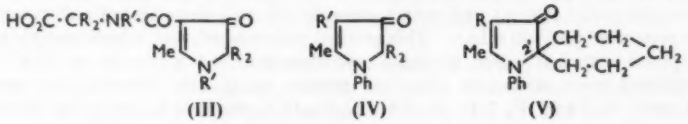
945. *The Conversion of Certain αα-Disubstituted N-Phenylglycines into 4-Oxo-1-phenyl-Δ²-pyrrolines.*

By R. J. S. BEER, W. T. GRADWELL, and (in part) W. J. OATES.

αα-Dialkyl-substituted *N*-phenylglycines (I) are converted by hot acetyl chloride into complex derivatives of type (III; R′ = Ph) which yield, on hydrolysis, basic 2-methyl-4-oxo-1-phenyl-Δ²-pyrrolines (IV; R′ = H).

WHEREAS *N*-phenylglycine is converted, under the conditions of the Dakin–West reaction, into *N*-phenylacetamidoacetone, the αα-disubstituted compound, α-anilino-α-methylpropionic acid (I; R = Me), is reported [1] to yield a mixture of complex products. We have examined the behaviour of several compounds of type (I; R = alkyl) towards hot acetyl chloride, which converts *N*-phenylglycine into the *N*-acetyldipeptide [2] (II). With the αα-disubstituted glycines no evidence of dipeptide formation has been obtained; the products, isolated in good yield, are believed to be 4-oxo-1-phenyl-Δ²-pyrroline derivatives

(I) $Ph\cdot NH\cdot CR_2\cdot CO_2H$ $Ac\cdot NPh\cdot CH_2\cdot CO\cdot NPh\cdot CH_2\cdot CO_2H$ (II)



(III) (IV) (V)

of type (III; R′ = Ph). In each case investigated the product, on acid hydrolysis, gave equivalent amounts of the original amino-acid and a basic oxopyrroline (IV; R′ = H), presumably formed by decarboxylation of an intermediate β-keto-acid (IV; R′ = CO_2H).

Thus 1-anilino*cyclo*hexanecarboxylic acid, after treatment with acetyl chloride and hydrolysis of the product, gave the spiran (V; R = H). This structure was assigned on the basis of the following observations: the compound reacts slowly with hydroxylamine in hot pyridine forming a monoxime; it contains one *C*-methyl group, readily yields a yellow monopiperonylidene derivative, and is oxidised by acid potassium permanganate to 1-acetanilido*cyclo*hexanecarboxylic acid. The analogous base derived from α-anilino-α-methylpropionic acid has been shown to be 2 : 5 : 5-trimethyl-4-oxo-1-phenyl-Δ²-pyrroline

[1] Buchanan, Reid, Thomson, and West, *J.*, 1957, 4427.
[2] Southwick, Dimond, and Stansfield, *J. Amer. Chem. Soc.*, 1956, **78**, 1608.

(IV; R = Me, R′ = H) by an independent synthesis. The method developed by Benary *et al.*[3] for the synthesis of 3-hydroxypyrroles was used, ethyl β-anilinocrotonate being condensed with α-bromo-α-methylpropionyl bromide and the resulting oxopyrroline ester (IV; R = Me, R′ = CO_2Et) hydrolysed to the acid which was decarboxylated smoothly at its melting point, giving the expected trimethyloxopyrroline. The ultraviolet absorption spectra of the spiran ($\lambda_{max.}$ in alcohol 316 mμ, ε 15,350) and the trimethyloxopyrroline ($\lambda_{max.}$ 316 mμ, ε 16,500; shoulder at 244 mμ, ε 1330) show the expected similarity to those recorded by Davoll[4] for various β-oxopyrrolines; 2 : 5-dimethyl-4-oxo-1-phenyl-Δ^2-pyrroline, for example, has absorption maxima at 246·5 (ε 2800) and 324·5 mμ (ε 16,200).

The heterocyclic nucleus of the spiran (V; R = H) has some of the properties of an activated aromatic system. Thus it is attacked rapidly in the cold by bromine in acetic acid, giving a monobromo-derivative which must have structure (V; R = Br) since it is oxidised by potassium permanganate to 1-acetanilido*cyclo*hexanecarboxylic acid. With excess of bromine, further substitution occurs. Treatment with nitrous acid yields a weakly basic, turquoise nitroso-compound which, by analogy with the bromo-derivative, is probably represented by formula (V; R = NO). The non-basic monoacetyl derivative, slowly formed from the oxopyrroline by the action of hot acetic anhydride and sodium acetate, is similarly formulated as (V; R = Ac).

Structure (III) for the products of the acetyl chloride reaction explains the observed results of hydrolysis, and such compounds could be formed by combination of two molecules of the acetylated amino-acids. It is possible that the reaction proceeds through the corresponding acid chloride since the same product (III; R = Me, R′ = Ph) was obtained from α-acetanilido-α-methylpropionic acid with acetyl chloride and with phosphorus pentachloride in hot benzene.

One compound which is probably of type (III) has been previously described. Accordinto to Steiger,[5] α-methyl-α-methylaminopropionic acid is converted in low yield, by acetic anhydride in hot acetic acid, into an oxopyrroline formulated as (III; R = R′ = Me). This compound is apparently hydrolysed slowly by boiling water to the original acid. A second hydrolysis product, believed to be a tetramethyloxopyrroline, was not obtained pure.

Experimental

Light petroleum used had b. p. 60—80°.

*5′-Methyl-3′-oxo-1′-phenyl*cyclo*hexane*spiro-*2′-Δ⁴-pyrroline* (V; R = H).—1-Anilino*cyclo*hexanecarboxylic acid[6] (6·0 g.) and acetyl chloride (30 ml.) were heated under reflux until a yellow solid separated (40—60 min.). This product was washed with a little acetyl chloride and then decomposed with hot water, giving a colourless *acid* (4·0 g.), m. p. *ca.* 214° (decomp.), which crystallised from alcohol in colourless prisms, m. p. 215° (Found, in a sample dried *in vacuo* at 100°: C, 74·0; H, 7·1; N, 5·8. $C_{30}H_{34}O_4N_2$ requires C, 74·1; H, 7·0; N, 5·8%). A suspension of the crude acid (2·0 g.) in concentrated hydrochloric acid (20 ml.) was heated on the steam-bath for 30 min., then diluted with water (40 ml.). The crystalline hydrochloride of 1-anilino*cyclo*hexanecarboxylic acid was collected and the filtrate made alkaline with 2N-aqueous sodium hydroxide, *5′-methyl-3′-oxo-1′-phenyl*cyclo*hexane*spiro-*2′-Δ⁴-pyrroline* (0·93 g.), m. p. 130—131°, being precipitated. This base crystallised from light petroleum in flat needles, m. p. 131—132° (Found: C, 79·9; H, 8·1; N, 5·9. $C_{16}H_{19}ON$ requires C, 79·7; H, 7·9; N, 5·8%).

1-Anilino*cyclo*pentanecarboxylic acid[6] (1·0 g.) was similarly converted into an *acid* (0·60 g.), plates (from aqueous alcohol), m. p. 225—256° (decomp.) (Found: C, 73·5; H, 6·6; N, 6·0. $C_{25}H_{30}O_4N_2$ requires C, 73·4; H, 6·5; N, 6·1%), which was converted by hydrochloric acid into

[3] Benary and Silbermann, *Ber.*, 1913, **46**, 1363; Benary and Konrad, *Ber.*, 1923, **56**, 44.
[4] Davoll, *J.*, 1953, 3802.
[5] Steiger, *Helv. Chim. Acta*, 1934, **17**, 555.
[6] Bain and Ritchie, *J.*, 1955, 4411.

XUM

5′-*methyl*-3′-*oxo*-1′-*phenyl*cyclo*pentane*spiro-2′-Δ^4-*pyrroline*, irregular plates (0·21 g.), m. p. 96° (from light petroleum) (Found: C, 79·2; H, 7·4; N, 6·2. $C_{15}H_{17}ON$ requires C, 79·3; H, 7·5; N, 6·2%).

α-Anilino-α-methylpropionic acid [7] (5·0 g.) with acetyl chloride yielded an *acid* which crystallised from aqueous alcohol in almost colourless prisms (3·1 g.), m. p. 235° (decomp.) (Found: C, 70·6; H, 6·7; N, 6·9. $C_{24}H_{26}O_4N_2$ requires C, 70·9; H, 6·5; N, 6·9%). The same product was obtained by the action of hot acetyl chloride or phosphorus pentachloride in hot benzene on α-acetanilido-α-methylpropionic acid.[1] Hydrolysis with hydrochloric acid gave 2 : 5 : 5-*trimethyl*-4-*oxo*-1-*phenyl*-Δ^2-*pyrroline* (IV; R = Me, R′ = H), prisms (from light petroleum), m. p. 88° (Found: C, 77·4; H, 7·5; N, 6·9. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5; N, 7·0%), $\lambda_{max.}$ 316 mμ (ε 16500), $\nu_{max.}$ (C=O) 1640 cm.$^{-1}$.

Reactions of 5′-*Methyl*-3′-*oxo*-1′-*phenyl*cyclo*hexane*spiro-2′-Δ^4-*pyrroline*.—The spiran, dissolved in ice-cold dilute hydrochloric acid, gave with nitrous acid a crystalline yellow hydrochloride, converted by the action of water, or more rapidly by sodium hydroxide, into the green *nitroso-compound* which crystallised from ethyl acetate–alcohol in turquoise needles, m. p. *ca.* 210° (after decomp.) (Found: N, 10·2. $C_{16}H_{18}O_2N_2$ requires N, 10·4%).

Heated on the steam-bath for 5 hr. with hydroxylamine hydrochloride in pyridine, the spiran yielded the *oxime*, needles (from light petroleum), m. p. 116—117° (Found: N, 10·7. $C_{16}H_{20}ON_2$ requires N, 10·9%).

With boiling acetic anhydride in the presence of sodium acetate the spiran was slowy converted into a non-basic *monoacetyl derivative*, needles (from benzene–light petroleum), m. p. 194° (Found: C, 76·9; H, 7·4; N, 4·8. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·4; N, 4·9%).

The *piperonylidene derivative*, prepared in alcohol containing a trace of sodium ethoxide, formed orange-yellow plates, m. p. 202—203°, from aqueous alcohol (Found: N, 3·6. $C_{24}H_{23}O_3N$ requires N, 3·7%).

Gradual addition of bromine (0·3 g.) in acetic acid (5 ml.) to a solution of the spiran (0·48 g.) in the same solvent (10 ml.) and dilution with water gave the *monobromo-derivative* (0·40 g.), prisms (from benzene–light petroleum), m. p. 156° (Found: C, 60·5; H, 5·9; N, 4·3. $C_{16}H_{18}ONBr$ requires C, 60·0; H, 5·6; N, 4·4%). With two mols. of bromine the spiran yielded a *dibromo-derivative*, yellow needles, m. p. 141° (from benzene–light petroleum) (Found: N, 3·5; Br, 40·8. $C_{16}H_{17}ONBr_2$ requires N, 3·5; Br, 40·1%). When three mols. of bromine were used, the product was a *tribromo-derivative*, yellow plates (from light petroleum), m. p. 136—137° (Found: N, 3·0; Br, 50·2. $C_{16}H_{16}ONBr_3$ requires N, 2·9; Br, 50·2%).

1% Aqueous potassium permanganate (100 ml.) was added slowly to a stirred solution of the spiran (1·0 g.) in 2N-sulphuric acid (50 ml.), and the following morning the resinous dark precipitate was collected, dried, and triturated with cold benzene. The residue, crystallised from benzene, formed colourless needles (80 mg.), m. p. 200—201°, undepressed on admixture with 1-*acetanilido*cyclo*hexanecarboxylic acid*, m. p. 200—201° (Found: N, 5·4. $C_{15}H_{19}O_3N$ requires N, 5·4%), which was prepared from the anilino-acid with acetic anhydride in pyridine. The acetanilido-acid (0·25 g.) was also obtained by a similar oxidation (in acetone) of the monobromopyrroline (1·0 g.).

Ethyl 2 : 5 : 5-*Trimethyl*-4-*oxo*-1-*phenyl*-Δ^2-*pyrroline*-3-*carboxylate* (IV; R = Me, R′ = CO_2Et).—α-Bromo-α-methylpropionyl bromide (5·6 g.) in ether (10 ml.) was added slowly with stirring to a cooled solution of ethyl β-anilinocrotonate (5·1 g.) and dry pyridine (2·0 g.) in ether (30 ml.). The mixture was kept at room temperature for 30 min. and the ether then removed by distillation. Two days later, the pasty yellow residue was treated with water, and the resulting orange-red oil (9·7 g.) isolated with ether. To a solution of this product in ice-cold methanol (20 ml.), potassium hydroxide (4·0 g.) dissolved in methanol (10 ml.) was added during 10 min. Stirring was continued for a further 15 min. with cooling and then for 30 min. at room temperature. After filtration, to remove potassium bromide, the methanol was evaporated and the residue treated with water and extracted with ether. The product, recrystallised from benzene–light petroleum, gave *ethyl* 2 : 5 : 5-*trimethyl*-4-*oxo*-1-*phenyl*-Δ^2-*pyrroline*-3-*carboxylate* as colourless plates (1·2 g.), m. p. 138° (Found: C, 69·9; H, 6·8; N, 5·4; OEt, 17·1. $C_{16}H_{19}O_3N$ requires C, 70·3; H, 7·0; N, 5·1; OEt, 16·5%).

2 : 5 : 5-*Trimethyl*-4-*oxo*-1-*phenyl*-Δ^2-*pyrroline*-3-*carboxylic Acid* (IV; R = Me, R′ = CO_2H). —The foregoing ester (0·50 g.) was heated under reflux with potassium hydroxide (1·25 g.) in ethanol (12·5 ml.) and water (12·5 ml.) for 3 hr. The ethanol was removed and the oxypyrroline

[7] Bucherer and Grolée, *Ber.*, 1906, **39**, 986.

acid (0·43 g.) precipitated with dilute hydrochloric acid. Crystallised from ethanol, it formed needles, m. p. *ca.* 220° (gas) (Found: C, 68·9; H, 6·0; N, 5·7. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1; N, 5·7%). This acid (0·30 g.), heated to its m. p. *in vacuo* (15 min.), gave in almost quantitative yield 2 : 5 : 5-trimethyl-4-oxo-1-phenyl-Δ^2-pyrroline, m. p. and mixed m. p. 88° (Found: C, 77·8; H, 7·7; N, 6·9%).

UNIVERSITY OF LIVERPOOL.

[*Received, July 17th*, 1958.]

---

946. *The Alkaloids of the Amaryllidaceae. Part III.* Hæmanthamine (Natalensine).*

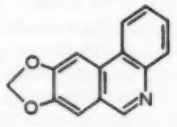
By F. L. WARREN and WINIFRED G. WRIGHT.

Hæmanthamine from *Haemanthus natalensis* is fully characterised and its formula elaborated to $C_{15}H_{13}N(CH_2O_2)(OMe)(OH)$ with a tertiary nitrogen atom and one double bond. Zinc-dust distillation gives methylenedioxyphenanthridine (I). Oxidation with potassium permanganate gives the series of compounds, 1 : 2 : 3 : 4-tetrahydro-3-oxo-6 : 7-methylenedioxy-*iso*quinoline-4-carboxylic acid (II), 4 : 5-methylenedioxy-2-oxalylbenzoic acid (III), and hydrastic anhydride (IV). Hofmann degradation gives *N*-methyl-2-phenylpiperonylamine (VIII) and 2-phenylpiperonaldehyde (V). These findings are accommodated in formula (X) for hæmanthamine.

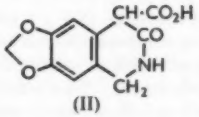
HÆMANTHAMINE, $C_{17}H_{19}O_4N$, was isolated by Boit [1] from *Haemanthus hybrid "King Albert"* and, as natalensine, from *H. natalensis* and *H. puniceus* by Wildman and Kaufman [2] and in our laboratories.[2] Since then it has been found in twenty-two natural species [3] and a large number of cultivated hybrids.[4]

In spite of its wide occurrence little was known about this alkaloid. There is one methoxyl and one methylenedioxy-group, and the other oxygen is present as a hydroxyl group (strong absorption in carbon tetrachloride at 3617 cm.[1] and an acetyl derivative). The formula may accordingly be expanded to $C_{15}H_{13}N(CH_2O_2)(OMe)\cdot OH$. The alkaloid is readily reduced to dihydrohæmanthamine, $C_{17}H_{21}O_4N$, so that there is one double bond. The nitrogen atom is tertiary in that hæmanthamine and dihydrohæmanthamine readily form methiodides.

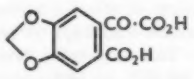
The alkaloid shows a band at 294 mμ (log ε 3·75) with a shoulder at 240 mμ (log ε 3·55), resembling safrole [$\lambda_{max.}$ 285 mμ (log ε 3·6), shoulder at 240 mμ (log ε 3·65)]. This and the fact that the ultraviolet extinction curve is unchanged after reduction show that the double bond is not conjugated with the benzene nucleus.



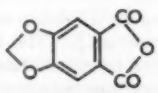
(I)



(II)



(III)



(IV)

Zinc-dust distillation of the alkaloid gave 6 : 7-methylenedioxyphenanthridine (I). Oxidation with potassium permanganate at 0° gave a crystalline compound, $C_{11}H_9O_5N$ (II), but at room temperature gave hydrastic acid isolated as its anhydride (IV), an acid,

* Part II, *J.*, 1957, 2537.

[1] Boit, *Chem. Ber.*, 1954, **87**, 1339.
[2] Wildman and Kaufman, *J. Amer. Chem. Soc.*, 1955, **77**, 1245; and references therein.
[3] Boit *et al.*, *Chem. Ber.*, 1954, **87**, 724; 1955, **88**, 1590; 1956, **89**, 163, 1129; 1957, **90**, 727, 1827, 2203.
[4] Boit, *ibid.*, 1957, **90**, 2197.

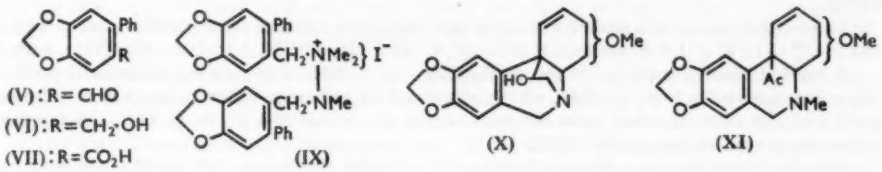
XUM

$C_{10}H_6O_7$, presumed to be 2-oxalyl-4 : 5-methylenedioxybenzoic acid (III), and a nitrogenous acid. The formulation of the last acid as 1 : 2 : 3 : 4-tetrahydro-3-oxo-6 : 7-methylenedioxy*iso*quinoline-4-carboxylic acid ((II) accounts for its non-basic character, for its being a possible intermediate in the formation of the other products (III) and (IV), and for its origin from a reduced phenanthridine.

The hydrastic anhydride was not obtained in sufficient quantities for analysis; but it showed similar melting-point characteristics and identical infrared spectra when compared with the product obtained from a similar oxidation of lycorine and with a synthetic sample kindly given by Drs. Reeve and Myers.

Hofmann degradation of hæmanthamine methiodide gave a mixture, which with acid readily gave red gums and a small quantity of *N*-methyl-4 : 5-methylenedioxy-2-phenylbenzylamine (VIII), as well as 4 : 5-methylenedioxy-2-phenylbenzaldehyde (V), isolated as its 2 : 4-dinitrophenylhydrazone, which changed its crystalline form when heated (discrepancies in the melting points of 2 : 4-dinitrophenylhydrazones have been commented on by other workers).[5] The same aldehyde is prepared by oxidation of 4 : 5-methylenedioxy-2-phenylbenzyl alcohol (VI) with potassium permanganate and on oxidation gave 4 : 5-methylenedioxy-2-phenylbenzoic acid (VII).

Formulation of the Hofmann product as (VIII) receives support from its oxidation to 4 : 5-methylenedioxy-2-phenylbenzaldehyde (V). When the secondary amine (VIII) was treated with methyl iodide there was formed in small quantities a compound, $C_{16}H_{18}O_2NI$, and a compound, $C_{17}H_{20}O_2NI,H_2O$ formulated as *NN*-dimethyl-4 : 5-methylenedioxy-2-phenylbenzylamine hydriodide and methiodide respectively, but the main product appeared from analyses to be a " semimethiodide " $(C_{15}H_{14}O_2N)_2,CH_3I,2H_2O$, formed presumably by the oxidation of the secondary amine to a tetrasubstituted hydrazine (IX), a type of oxidation previously observed by Goldschmidt and Voeth.[6]



The elimination of two carbon atoms in the Hofmann reaction is to be understood if hæmanthamine has structure (X). The initial product of the reaction would be a base which would be expected to become aromatic by eliminations similar to those envisaged for Hofmann degradation of tazettine.[7] The aldehyde (V) would result from the fission of the hydroxy-amine formed by oxidation of the secondary amine (VIII). This formulation (X) shows the double bond and the methoxy-group in the same position as in tazettine,[7] with which hæmanthamine is closely associated in several species. Further, the large change in molecular rotation of the base and its methiodide after hydrogenation indicates the close proximity of the double bond to an asymmetric centre. The isolation of the intermediate oxidation product (II) supports structure (X), for the oxidation of the *iso*quinoline nucleus at position 4 would be arrested by the absence of a hydrogen atom there. The same structure has been advanced by Fales and Wildman on different evidence.[8]

[5] Campbell, *Analyst*, 1936, **61**, 391; Bredenck and Fritzche, *Ber.*, 1932, **65**, 1833; 1937, **70**, 802; Lange and Houtman, *Rec. Trav. chim.*, 1946, **65**, 891.
[6] Goldschmidt and Voeth, *Annalen*, 1924, **435**, 265.
[7] Wiesner and Valenta, *Chem. and Ind.*, 1956, R 36; Ikeda, Taylor, Tsuda, and Uyeo, *Chem. and Ind.*, 1956, 411.
[8] Fales and Wildman, *Chem. and Ind.*, 1958, 561.

Experimental

Extraction.—The sliced bulbs of *H. natalensis* were extracted once with alcohol, dried (1100 g.), ground, and re-extracted with alcohol. The extract was concentrated, steam-distilled, made alkaline, and extracted with chloroform. The chloroform extract was passed through an alumina column, the chloroform eluate separated, and then the residual alkaloids were washed out with 1 : 19 ethanol–chloroform.

The chloroform eluate gave crystals (0·94 g.) which were washed with cold acetone and crystallised twice from acetone, to give hæmanthamine, m. p. 204·5° (Boit [1] and Wildman and Kaufman [2] give m. p. 200—201° and 199—200° respectively) (Found: C, 68·3, 68·4; H, 6·3, 6·6; N, 4·1, 4·6; OMe, 11·0; active H, 0·35. Calc. for $C_{17}H_{19}O_4N$: C, 67·8; H, 6·3; N, 4·7; OMe, 10·3; 1 active H, 0·35%). The *picrate* formed needles (from water), m. p. 220—222°, with change in crystalline form at 150° and without loss of weight at 160° (Found: C, 51·2; H, 4·3; N, 10·7. $C_{23}H_{22}O_{11}N_4,\frac{1}{2}H_2O$ requires C, 51·2; H, 4·3; N, 10·4%) [Boit gives m. p. 221° (unanalysed)], and the *styphnate*, separating from hot water, had m. p. 148—151° (Found: C, 50·2; H, 4·2. $C_{23}H_{22}O_{12}N_4$ requires C, 50·0; H, 4·2%).

The ethanol–chloroform eluate yielded a mixture of alkaloids (1·0 g.), and a water-soluble hygroscopic gum (8·3 g.).

Acetylhæmanthamine Picrate.—Hæmanthamine and excess of acetic anhydride were refluxed for 30 min. The product worked up in the usual way gave an oil, b. p. 150°/0·3 mm. This gave *acetylhæmanthamine picrate* which, recrystallised twice from ethanol, yielded needles, m. p. 175°, recrystallising without loss of weight at 178°, and remelting at 189° (Found: C, 52·5; H, 4·6. $C_{25}H_{24}O_{12}N_4$ requires C, 52·4; H, 4·2. $C_{25}H_{24}O_{12}N_4$ requires C, 52·4; H, 4·2%).

Hæmanthamine Methiodides.—Hæmanthamine (2·25 g.) in chloroform (40 ml.) and methyl iodide (5 ml.) were refluxed on a water-bath for 30 min. and set aside overnight. The crystalline deposit was boiled in water with Norit and filtered, to give, while still hot, *hæmanthamine methiodide* as needles, m. p. 204—206°, $[\alpha]_D^{22}$ +13·8° (*c* 2 in methanol) (Found: C, 47·1; H, 4·8; N, 3·0; OMe, 6·4; NMe, 5·5. $C_{18}H_{22}O_4NI,H_2O$ requires C, 46·8; H, 5·2; N, 3·0; OMe, 6·7; NMe, 6·3%).

The mother-liquor, set aside for some hours, deposited another *form* (needles), m. p. 192—194°, $[\alpha]_D^{22}$ +13·4° (*c* 1·6 in methanol) (Found: C, 47·3; H, 5·0; N, 3·1; OMe, 6·3; NMe, 5·5%).

A methyl alcohol solution of the methiodide, m. p. 204—206°, on evaporation deposited the substance (0·5 g.), m. p. 204°, which, dissolved in sufficient water to keep it in solution until cool and then set aside, gave successive crops of crystals (0·4 g.), m. p. 192°. A mixture of the two forms had m. p. 190—200°.

Dihydrohæmanthamine.—Hæmanthamine in ethanol, hydrogenated in the presence of Adams's catalyst, absorbed 0·98 mol. of hydrogen. The filtered solution, allowed to evaporate, gave *dihydrohæmanthamine* as needles, m. p. 222—223°, $[\alpha]_D^{24}$ +67·0 (*c* 0·8 in ethanol) (Found: C, 67·3; H, 7·0. $C_{17}H_{21}O_4N$ requires C, 67·3; H, 6·9%). The *picrate* (from ethanol) had m. p. 208—210° (Found: C, 51·9; H, 4·8; N, 11·81. $C_{23}H_{24}O_{11}N_4$ requires C, 51·9; H, 4·5; N, 10·5%).

Dihydrohæmanthamine (2 g.) and methyl iodide (4 ml.) were refluxed for 30 min. and allowed to cool slowly overnight. Larger prisms of a *solvated methiodide* were deposited, which lost solvent of crystallisation at 178° for 2 hr. (Found: Loss of weight, 22. $C_{18}H_{24}O_4NI,CHCl_3$ requires $CHCl_3$, 21%). There was no loss in weight after two hours' heating at 105°, but the chloroform was immediately freed in boiling water. This substance was dissolved in water and set aside overnight, to give large oblong prisms of a *sesquihydrate* which rapidly became opaque in air and lost solvent at 20°/0·2 mm. (Found: Loss of wt., 2, 2·5. $C_{18}H_{24}O_4NI,1\frac{1}{2}H_2O$ requires $\frac{1}{2}H_2O$, 1·9%), leaving *dihydrohæmanthamine methiodide monohydrate*, m. p. 186°, $[\alpha]_D^{21}$ +50° (*c* 2·9 in methanol) (Found: C, 46·7; H, 5·72; OMe, 8·5; NMe, 6·5. $C_{18}H_{24}O_4NI,H_2O$ requires C, 46·6; H, 5·65; OMe, 6·7; NMe, 6·3%). This substance in water deposited, on cooling, large pointed prisms of a fourth *solvate*, which became slightly opaque in air and lost solvent of crystallisation at 20°/0·2 mm. (Found: Loss of wt., 5·8, 4·6. $C_{18}H_{24}O_4NI,2\frac{1}{2}H_2O$ requires $1\frac{1}{2}H_2O$, 5·51%), giving the monohydrate, m. p. 200°, $[\alpha]_D^{20}$ +57·7° (*c* 2·9 in methanol) (Found: C, 47·3; H, 5·3; OMe, 7·2; NMe, 5·9%).

Distillation of Hæmanthamine with Zinc Dust.—Hæmanthamine (0·1 g.) in zinc dust (3 g.) was gently distilled through a layer of heated zinc dust. The cooled mixture was lixiviated with alcohol, the alcohol evaporated, and the residue in benzene chromatographed over alumina.

The first eluates gave oils, and the later fractions a solid which sublimed at 120°/2 mm., to give **6 : 7-methylenedioxyphenanthridine** as needles, m. p. 149°, subliming at 120°. The picrate was sublimed at 130°/0·2 mm. and recrystallised from ethanol as needles, m. p. 290° (Found: C, 52·7; H, 2·7. Calc. for $C_{20}H_{12}O_9N_4$: C, 53·1; H, 2·7%). Kondo *et al.*[9] give m. p. 142° and for its picrate m. p. 257°. The picrate, observed under the microscope, started to sublime to a yellow oil at 257°, and the residual crystals showed m. p. 290°, f. p. 288°, and decomposed at 291°.

Oxidation with Potassium Permanganate.—(*a*) Hæmanthamine (2·53 g.) was dissolved in 0·1N-hydrochloric acid, the solution was neutralised to pH 8 with sodium hydroxide and cooled to 0°, and 1% potassium permanganate solution (450 ml.) was added slowly. The solution was acidified and extracted with ether. The ether solution gave a wax which recrystallised from benzene and sublimed at 130°/760 mm., giving **1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*methylenedioxy*-3-*oxo*isoquinoline-4-*carboxylic acid*** as diamond-shaped needles (17 mg.), acid to litmus, not to Congo Red. Twice resublimed at 130°/0·2 mm. it gave needles, changing form at 190—200°, m. p. 220° (Found: C, 55·9; H, 3·5; N, 6·35. $C_{11}H_9O_5N$ requires C, 56·2; H, 3·8; N, 6·0%).

(*b*) Hæmanthamine (0·84 g.) was dissolved in 0·1N-hydrochloric acid (35 ml.), and 0·1N-sodium hydroxide added until the solution had pH 9. Potassium permanganate was run in with stirring until an excess was present (406 ml.). The solution was filtered, set aside overnight, extracted with ether, acidified to pH 2, and re-extracted with ether. The second ethereal extract gave a product which sublimed at 109°/760 mm. to crystals, m. p. 173—174° (in capillary tube). It showed similar m. p. characteristics to, and identical infrared spectra with, hydrastic anhydride, obtained by similar oxidation of lycorine and also a synthetic sample kindly sent by Drs. Reeve and Myers. For hydrastic anhydride Kondo, Katsura, and Ogami [9] give m. p. 173°, and Reeve and Myers [10] give m. p. 179—180°. Observed under a microscope, the crystals changed form at 140° and, when they had been held at that temperature until the change was complete, the m. p. was 185—186°, crystallisation occurred immediately after melting, and remelting at 190°.

After sublimation of the hydrastic anhydride the residue was dissolved in aqueous sodium hydrogen carbonate, decolorised with Norit, filtered, acidified, and extracted with ether. The solution was concentrated, light petroleum added, and the whole set aside, affording **4 : 5-*methylenedioxy*-2-*oxalylbenzoic acid***, m. p. 206° (Found: C, 50·3; H, 2·5. $C_{10}H_6O_7$ requires C, 50·4; H, 2·5%).

The ether–light petroleum solution was chromatographed over alumina, to give crystals changing form at 190—200°, and m. p. 220°, undepressed on admixture with the compound from first oxidation.

Hofmann Degradation of Hæmanthamine Methiodides.—Hæmanthamine methiodide (2·9 g.), m. p. 188—192°, water (50 ml.), and silver oxide [from silver nitrate (10 g.)] were stirred on a water-bath for 2 hr., then filtered, and evaporated under reduced pressure. The dark brown solid was heated at 100°/0·2 mm. for 30 min. and lixiviated with benzene. The residue dissolved in water and gave a ***reineckate*** (Found: N, 14·7. $C_{21}H_{25}O_4N_7S_4$ requires N, 15·8%). The red benzene solution was extracted with dilute hydrochloric acid until the extract gave no reaction with Meyer's reagent. A copious red oil separated with each extraction and was collected in acetone. The clear acid extract was treated stepwise with sodium hydrogen carbonate. A red tar and then a red solid separated at pH 2—4 and were filtered off separately. The solution was set aside for two days, and filtered from the red deposit. The filtrate was treated stepwise with sodium hydrogen carbonate to give a copious creamy precipitate at pH 6 and then at pH 8 an oil. Sufficient acid was added to dissolve the oil, the solution filtered and made alkaline with sodium hydrogen carbonate, and the precipitated oil extracted with ether. The ether extract gave **N-*methyl*-4 : 5-*methylenedioxy*-2-*phenylbenzylamine*** as a colourless oil (Found: C, 74·2; H, 6·45; N, 5·8. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·3; N, 5·8%). The ***hydrochloride*** crystallised from acetone in needles (0·4 g.), m. p. 160°. The crystals lost water in air and completely at 20°/0·2 mm. and were dried at 100°/0·2 mm. (Found: Loss of wt., 6·05. $C_{15}H_{16}O_2NCl,H_2O$ requires H_2O, 6·1. Found, for anhydrous material: C, 64·7, 64·5; H, 5·9, 5·9; N, 5·0, 4·9; Cl, 13·0, 13·0. $C_{15}H_{16}O_2NCl$ requires C, 64·8; H, 5·8; N, 5·0; Cl, 12·8%). The hydrochloride in water, with aqueous picric acid, gave the ***picrate***, needles, m. p. 148—150°, which recrystallised from hot water as needles, m. p. 95—97°, becoming completely crystalline at 120°, and remelting at 157°

[9] Kondo, Katsura, and Ogami, *J. Pharm. Soc. Japan*, 1940, **60**, 619.
[10] Reeve and Myers, *J. Amer. Chem. Soc.*, 1951, **73**, 1371.

XUM

(Found, for substance, m. p. 157°: C, 53·0; H, 3·7. $C_{21}H_{18}O_9N_4$ requires C, 53·5; H, 4·1. Found, for substance, m. p. 97°: C, 52·3; H, 4·55; N, 11·3. $C_{21}H_{18}O_9N_4,H_2O$ requires C, 51·7; H, 4·13; N, 11·5%).

4 : 5-*Methylenedioxy*-2-*phenylbenzaldehyde* 2 : 4-*Dinitrophenylhydrazone*.—This substance was obtained on addition of 2 : 4-dinitrophenylhydrazine hydrochloride in alcohol to an alcoholic solution of (i) the brown impurities obtained by washing the hydrochloride of the methine with acetone, (ii) the benzene solution of the Hofmann degradation product, and (iii) the distillate obtained by heating the red oil produced during the Hofmann reaction at 170°/0·2 mm. The colloidal solution formed was evaporated to dryness, dissolved in benzene, and passed through alumina. The first eluate with benzene gave **4 : 5-*methylenedioxy*-2-*phenylbenzaldehyde* 2 : 4-*dinitrophenylhydrazone*** which crystallised from benzene in orange needles. The m. p. of the compound depended on the rate of heating. Rapid heating gave m. p. 280°. On a microapparatus it sublimed above 230° to give a mixture of needles and deep red diamond-shaped crystals. At 270—275° the substance slowly changed from the orange needles to the diamond-shaped crystals, and, if subsequent heating was slow enough to complete the change before the m. p. of the mixture was reached, the resultant compound had m. p. 297° (Found: C, 59·6; H, 3·5; N, 14·2. $C_{20}H_{14}O_8N_4$ requires C, 59·1; H, 3·5; N, 13·8%).

Oxidation of **N-*Methyl*-4 : 5-*methylenedioxy*-2-*phenylbenzylamine*** (VIII).—A solution of the hydrogen amine (VIII) hydrochloride (500 mg.) in water was made alkaline with sodium carbonate and extracted with ether. The extract gave an oil which was treated in acetone with a 1% solution of potassium permanganate in acetone (40 ml., 4 equivs. of oxygen) at 0°. After 12 hr. the solution was filtered, decolorised with a drop of formaldehyde, and evaporated. The residue crystallised from light petroleum, to give 4 : 5-methylenedioxy-2-phenylbenzaldehyde in needles (210 mg.), m. p. 89°, subliming at 75° (Found: C, 74·2; H, 4·55. Calc. for $C_{14}H_{10}O_3$: C, 74·3; H, 4·5%). Späth and Kahovec [11] give m. p. 87°. It gives with concentrated sulphuric acid a deep green colour, and a blue precipitate. Piperonaldehyde gives a green colour only, with sulphuric acid. The 2 : 4-dinitrophenylhydrazone had a m. p. which varied as reported above, and an infrared spectrum identical with that from the product of the Hofmann reaction above and with that from the oxidation product of 4 : 5-methylenedioxy-2-phenylbenzyl alcohol.

Reaction of **N-*Methyl*-4 : 5-*methylenedioxy*-2-*phenylbenzylamine* with *Methyl Iodide*.**—(*a*) A solution of the amine hydrochloride (0·2 g.) in water was basified with sodium hydrogen carbonate and extracted with ether. The oil so obtained was dissolved in chloroform, and methyl iodide (2 ml.) was added. Iodine was immediately liberated. The solution was refluxed for 1 hr. and evaporated to a gum which solidified on lixiviation with boiling benzene–alcohol (70 : 30) (three times), to leave a white solid, the organic solvent becoming yellow. The yellow solution obtained by the first boiling was concentrated to give **NN-*dimethyl*-4 : 5-*methylenedioxy*-2-*phenylbenzylamine hydriodide*** as hexagonal crystals (8 mg.), m. p. 206° (Found: C, 49·8; H, 5·02. $C_{16}H_{16}O_2NI$ requires C, 50·1; H, 4·74%).

The white solid was dissolved in alcohol (1 ml.), and one drop of benzene added to give crystallisation immediately in needles (10 mg.), m. p. 144—146°.

(*b*) The amine (250 mg.) in ether and methyl iodide were set aside for one day in the dark at 0°. The gummy precipitate was dissolved in a little alcohol, and a few drops of benzene were added, and the crystalline solid (120 mg.) was recrystallised by the same procedure, to give **1 : 2-*dimethyl*-1 : 2-*di*-(4 : 5-*methylenedioxy*-2-*phenylbenzyl*)*hydrazine monomethiodide***, m. p. 144° (Found: C, 56·4, 56·3; H, 5·6, 5·3. $C_{31}H_{31}O_4N_2I,2H_2O$ requires C, 56·5; H, 5·35%). The mother liquor therefrom was evaporated to dryness and lixiviated with benzene, to leave a residue, m. p. 204°, undepressed by the substance, m. p. 206°, obtained in the first preparation. The benzene solution slowly deposited **NNN-*trimethyl*-4 : 5-*methylenedioxy*-2-*phenylbenzyl*-*ammonium iodide*** as one large hexagonal crystal (11·2 mg.), m. p. 132—134° (Found: C, 49·0; H, 4·8. $C_{17}H_{20}O_2NI,H_2O$ requires C, 49·2; H, 5·3%).

The authors gratefully acknowledge grants from the South African C.S.I.R.

Department of Chemistry and Chemical Engineering, University of Natal, Durban and Pietermaritzburg. [*Received, July 22nd*, 1958.]

[11] Späth and Kahovec, *Ber.*, 1934, **67**, 1501.

947. *The Alkaloids of the Amaryllidaceae. Part IV.* The Alkaloids of* Brunsvigia cooperi *Baker.*

By L. J. Dry, (Miss) M. Poynton, M. E. Thompson, and F. L. Warren.

Two new alkaloids, brunsvigine and brunsvinine, are isolated from *Brunsvigia cooperi* Baker bulbs collected in summer, lycorine replacing brunsvinine in bulbs collected in late autumn. Crinamine is also isolated throughout. Brunsvigine is shown to be isomeric with lycorine, possessing the same groups as the latter, but differing from lycorine in ease of dehydration and in the behaviour of the dihydro-derivative.

No member of the *Brunsvigia* genus of the family Amaryllidaceae has so far been examined chemically. *Brunsvigia rosea* (Lam.), investigated by Wildman and his co-workers,[1] has been referred back to *Amaryllis rosea* (*A. belladonna* Linn.[2]). The bulbs of *B. cooperi* Baker are now found to contain two new alkaloids: brunsvigine, $C_{16}H_{17}O_4N$, as the main alkaloid, and brunsvinine, $C_{17}H_{19}O_4N$, in very small quantities in bulbs collected during early summer, becoming replaced, seemingly completely so, by lycorine towards autumn. A fourth alkaloid, identified as crinamine,[1,3] was found in more or less constant yield throughout.

Brunsvigine, its hydrochloride, and its picrate all form various solvates. Ready formation of a methiodide showed the nitrogen to be tertiary. The presence of two hydroxy-groups was shown by formation of diacetylbrunsvigine, and a broad band at 3475 cm.$^{-1}$ in the infrared spectrum of the alkaloid indicated that the hydroxy-groups were associated. That the hydroxy-groups are neighbours was indicated by reaction with one mol. of periodic acid in acid solution although no reaction was observed in neutral medium; according to Price and Knell's findings [4] this could mean that the hydroxy-groups are *trans*-oriented. The resulting oxidation product reduced Fehling's solution but failed to crystallise or to yield a tractable picrate or methiodide. Dihydrobrunsvigine similarly reacted with one mol. of periodic acid but also failed to yield a tractable dialdehyde. It is of interest that lycorine consumes ~1 mol. of periodic acid in acid medium in 6 days, and dihydrolycorine reacts more slowly.

Berzoa's test [5] showed the presence of a methylenedioxy-group. Permanganate oxidation of brunsvigine gave a small amount of hydrastic acid.[6]

Catalytic reduction of brunsvigine gave a dihydro-derivative, whose ultraviolet spectrum [$\lambda_{max.}$ 235 and 294 mμ (log ε 3·49 and 3·68 respectively)] closely resembled that of brunsvigine [$\lambda_{max.}$ 242 and 292 mμ (log ε 3·61 and 3·69 respectively)], which suggested that the ethylenic bond was not conjugated with the aromatic ring.[7] At the lower wavelength hydrogenation causes a small decrease in $\lambda_{max.}$ and in ε, which in comparison with the shifts observed by Leonard and Locke [8] does not indicate conclusively an αβ-unsaturated amine. A weak band at 1689 cm.$^{-1}$ in the infrared spectrum of brunsvigine confirmed the ethylenic bond. Conversion into the hydrochloride resulted in the appearance of a strong band at 1623 cm.$^{-1}$ in place of the band at 1689 cm.$^{-1}$, a shift in the opposite direction to that observed by Leonard and Gash [9] on conversion of an αβ-unsaturated amine into its

* Part III, preceding paper.

[1] Mason, Puschett, and Wildman, *J. Amer. Chem. Soc.*, 1955, **77**, 1253.
[2] Index Kewensis, Clarendon Press, London, Suppl. II, 1941—1950, p. 36.
[3] Tanaka, *J. Pharm. Soc. Japan*, 1937, **57**, 139.
[4] Price and Knell, *J. Amer. Chem. Soc.*, 1942, **64**, 552.
[5] Berzoa, *Analyt. Chem.*, 1954, **26**, 1971.
[6] Späth and Kabovec, *Ber.*, 1934, **67**, 1504.
[7] Kondo and Katsura, *Ber.*, 1940, **73**, 1424.
[8] Leonard and Locke, *J. Amer. Chem. Soc.*, 1955, **77**, 437.
[9] Leonard and Gash, *ibid.*, 1954, **76**, 2781.

XUM

salt. These authors found, however, that with a mixture of two isomeric α-substituted αβ-unsaturated *N*-methylpyrrolines a shift in the same direction occurred as was observed in brunsvigine. Brunsvigine further showed a medium band at 798 cm.$^{-1}$ and a weaker band at 820 cm.$^{-1}$, both of which may be assigned [10] to out-of-plane ethylenic C–H deformation vibrations for compounds of the type RR'C=CHR''. Both bands disappeared upon hydrogenation (although the 820 cm.$^{-1}$ band may have been obscured in the spectrum of dihydrobrunsvigine by a strong band at 828 cm.$^{-1}$). Brunsvigine further exhibited medium bands at 830, 868, and 730 cm.$^{-1}$, the last two being absent from the spectrum of dihydrobrunsvigine. These findings parallel those of Govindachari and Thyagarajan [11] who assigned a trisubstituted ethylenic bond in a βγ-position to the nitrogen atom to lycorine. Upon conversion into the hydrochloride, however, the lycorine bands at 1716 and 1620 cm.$^{-1}$ shifted to 1682 and 1646 cm.$^{-1}$ respectively, a behaviour not characteristic of βγ-unsaturated amines.[9] The ethylenic bonds in brunsvigine and lycorine appear therefore to be closely similar.

Brunsvigine resisted dehydration by alumina under conditions described by Cook, Loudon, and McCloskey,[12] and attempted dehydration by boric acid (O'Connor and Nace [13]) gave no recognisable products. Whereas according to Kondo and Katsura,[14] dihydrolycorine methohydroxide resisted both Hofmann and Emde degradation, dihydrobrunsvigine methohydroxide readily underwent Hofmann degradation to a methine without loss of the alcoholic groups.

An interesting feature of the bases of *Brunsvigia cooperi* isolated is the possession of one methoxy-group by both brunsvinine and crinamine, each $C_{17}H_{19}O_4N$, whereas neither brunsvigine nor lycorine, each $C_{16}H_{17}O_4N$, has a methoxy-group. Since brunsvigine possesses the same groups as lycorine, a simple relation between the four alkaloids of *B. cooperi* is probable.

Experimental

Microanalyses are by Yvonne Merchant, and spectroscopic data by Dr. E. C. Leisegang and M. von Klemperer.

Extraction.—Bulbs of *Brunsvigia cooperi* Baker collected in May at Dargle, Natal, were sliced and extracted several times with boiling ethanol for 3—5 hr. (wt. of material after extraction and drying, 3·1 kg.). The solvent was removed by flash-evaporation *in vacuo*, residual alcohol removed by steam, and the residue filtered from a small quantity of gum. The acidified filtrate was extracted with ether (which removed a further quantity of non-basic gum), made alkaline with potassium carbonate, and extracted repeatedly with pentyl alcohol. The extracts were dried (Na_2SO_4), concentrated to 200 ml., diluted with ether (600 ml.), and filtered from a large quantity of gummy alkaloid. The filtrate, after removal of the ether and further concentration *in vacuo*, deposited nearly pure brunsvigine (7 g.).

The alkaloidal mixture, precipitated by ether from the pentyl alcohol concentrate, was extracted with boiling chloroform and filtered from some resin. This extract, combined with the residue obtained from the mother-liquor of the brunsvigine crop, was chromatographed on alumina. Elution with chloroform gave, after an initial small gum, nearly pure *crinamine* (1·0 g.) which crystallised in flat needles from chloroform–ether or fine needles from acetone, and had m. p. 196°, $[\alpha]_D^{20}$ +100° (*c* 1 in ethanol) (Found: C, 67·55, 67·7; H, 6·6, 6·5; N, 4·5, 4·3. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·4; N, 4·65%). The *picrate* crystallised immediately from alcohol or water in small needles, m. p. 272° (decomp.) not raised on recrystallisation from methanol (Found: C, 52·2; H, 4·5; N, 10·1. $C_{23}H_{22}O_{11}N_4$ requires C, 52·1; H, 4·2; N, 10·6%). The *methiodide* crystallised in long, fine needles (from methanol), m. p. 265° (Found: C, 46·45; H, 5·4. $C_{18}H_{22}O_4NI,H_2O$ requires C, 46·9; H, 5·2%).

[10] Sheppard and Simpson, *Quart. Rev.*, 1952, **6**, 27.
[11] Govindachari and Thyagarajan, *Chem. and Ind.*, 1954, 374.
[12] Cook, Loudon, and McCloskey, *J.*, 1954, 4176.
[13] O'Connor and Nace, *J. Amer. Chem. Soc.*, 1955, **77**, 1578.
[14] Kondo and Katsura, *Ber.*, 1939, **72**, 2083.

XUM

Further elution with chloroform gave lycorine in short, stout needles (0·34 g.), m. p. and mixed m. p. 275° (decomp.) (from water). It gave a hydrochloride, m. p. and mixed m. p. 218°, and a picrate, m. p. 196°. Continued elution with chloroform gave small amounts of brunsvigine, m. p. 240° (from water), but this alkaloid was better removed from the column by extrusion and extraction with boiling ethanol. The lower, colourless portion of the column gave nearly pure brunsvigine (4·2 g.), m. p. 240° after one recrystallisation from water, while the upper portion gave a less pure product (2 g.) from which some brunsvigine (0·5 g.) was obtained by repeated crystallisation from water and acetone.

Bulbs collected in November gave, instead of lycorine after elution of crinamine, a small amount (*ca.* 150 mg.) of *brunsvinine*, m. p. 140—142° after recrystallisation from acetone, 202° after heating at 100°/1 mm. (Found: C, 67·3; H, 6·6; N, 4·6; OMe, 8·8. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·4; N, 4·65; OMe, 10·3%). The picrate, m. p. 67—69°, crystallised in nodules of small plates from ethanol.

Brunsvigine crystallised from acetone as *semihydrate* in needles, m. p. 243—245° (Found: C, 65·2; H, 6·4; N, 5·0. $C_{16}H_{17}O_4N,0{\cdot}5H_2O$ requires C, 64·9; H, 6·1; N, 4·7. Found, after drying at 100°/0·5 mm.: C, 66·85; H, 5·7. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 6·0%). Brunsvigine sublimed at 180°/0·1 mm., giving needles of the anhydrous *form*, m. p. 243°, $[\alpha]_D^{20}$ −76·6° (*c* 1 in ethanol) (Found: C, 66·8; H, 6·1%). Triangular prisms of a *sesquihydrate*, melting and depositing needles at 140—150°, were obtained from water (Found: C, 60·7; H, 6·5. $C_{16}H_{17}O_4N,1{\cdot}5H_2O$ requires C, 61·1; H, 6·4%). The molecular weight was determined from the ultraviolet extinction coefficient of the picrate (Found: *M*, 294. $C_{16}H_{17}O_4N$ requires *M*, 287).

Brunsvigine Derivatives.—The *picrate* crystallised from water or ethanol as yellow needles, m. p. 190° (Found: C, 50·9, 51·0; H, 4·3, 4·3; N, 11·2. $C_{22}H_{20}O_{11}N_4$ requires C, 51·2; H, 3·9; N, 10·9%). On other occasions yellow needles of a *form*, m. p. 219°, were obtained (Found: C, 51·4; H, 4·4%). The *methiodide* crystallised from ethanol in colourless, fine needles, m. p. 252°, $[\alpha]_D^{20}$ +29·8° (*c* 1 in ethanol) (Found: C, 46·4; H, 4·3. $C_{17}H_{20}O_4NI,0{\cdot}5H_2O$ requires C, 46·6; H, 4·8%). The *hydrochloride* was obtained in a hydrated form, m. p. 218—220°, by the evaporation of an aqueous solution (Found: C, 55·1; H, 6·1; Cl, 10·3. $C_{16}H_{18}O_4NCl,1{\cdot}5H_2O$ requires C, 54·8; H, 6·0; Cl, 10·1%). When prepared in ethanol by the addition of either concentrated hydrochloric acid or gaseous hydrogen chloride and by recrystallisation from ether–ethanol, a second *hydrate*, m. p. 245°, was obtained (Found after drying at 130°/1 mm.: C, 57·6; H, 6·05; Cl, 10·65. $C_{16}H_{18}O_4NCl,0{\cdot}5H_2O$ requires C, 57·8; H, 5·7; Cl, 10·7%).

Brunsvigine (110 mg.) in pyridine (3 ml.) was refluxed with acetic anhydride (3 ml.) for 3 hr. Methanol was added, and the mixture boiled for 5 min. and evaporated under reduced pressure to a brown oil which was filtered in benzene through alumina and on evaporation gave a solid *diacetate*. This crystallised from ether–light petroleum in needles, m. p. 184° (Found: C, 64·7; H, 6·0; Ac, 28·6. $C_{20}H_{21}O_6N$ requires C, 64·7; H, 5·7; Ac, 29·6%).

Dihydrobrunsvigine.—Brunsvigine (1 g.) in warm water (60 ml.) and N-hydrochloric acid (4 ml.) was hydrogenated in the presence of Adams's catalyst, 175 ml. hydrogen being absorbed in 6 hr. The solution was filtered, made alkaline with sodium hydrogen carbonate, and extracted with pentyl alcohol (3 × 40 ml.), which gave a gum, solidifying on addition of a little acetone. The solid recrystallised from acetone to give *dihydrobrunsvigine* as colourless needles, m. p. 203°, $[\alpha]_D^{20}$ +10·6° (*c* 1 in ethanol) (Found: C, 66·3; H, 6·6. $C_{16}H_{19}O_4N$ requires C, 66·4; H, 6·6%). On evaporation of the basic solution after extraction with pentyl alcohol, more dihydrobrunsvigine was recovered. The picrate crystallised from water as yellow needles, m. p. 218° (Found: C, 50·3; H, 4·75. $C_{22}H_{22}O_{11}N_4$ requires C, 51·0; H, 4·3%). The methiodide crystallised from acetone in nodules or stout needles, m. p. 186°, during 24 hr.

Periodic Acid Oxidation.—The oxidation of brunsvigine was typical of the procedure: brunsvigine (sesquihydrate; 100 mg., 1 mol.) in aqueous 0·14% periodic acid (60 ml., 1·2 mol.) and 2N-sulphuric acid (1 ml.) was set aside for 1 hr. at room temperature after which no further consumption of periodic acid occurred (Found: 0·97 mole of periodic acid consumed).

Dihydrobrunsviginemethine.—Dihydrobrunsvigine methiodide (0·3 g.) in water (50 ml.) was stirred with silver oxide (0·3 g.) until the solution was free from iodide. The filtrate was evaporated to dryness at 50°/30 mm., and the glassy residue heated at 97° *in vacuo* for 30 min. and extracted with boiling dry ether (100 ml.) which gave, on concentration, needles of *dihydrobrunsviginemethine*, m. p. 156°, not raised on recrystallisation from ether (Found: C, 67·35; H, 7·2; N, 4·6; NMe, 9·3. $C_{17}H_{21}O_4N$ requires C, 67·3; H, 7·0; N, 4·6; NMe, 9·6%). The

bulk of the ether-insoluble methohydroxide was converted into the methine by further heating. Dihydrobrunsviginemethine methiodide crystallised slowly from acetone in nodules of prisms, m. p. 130° (fast heating) or 179° (slow heating) [mixed m. p. with dihydrobrunsvigine methiodide 160—170° (slow heating)].

The authors acknowledge bursaries (to M. P. and M. E. T.) and grants from the S.A.C.S.I.R.

DEPARTMENT OF CHEMISTRY AND CHEMICAL TECHNOLOGY, UNIVERSITY OF NATAL, PIETERMARITZBURG, S. AFRICA. [*Received, July 22nd*, 1958.]

---

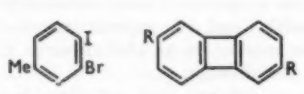
948. *The Reaction of 3-Bromo-4-iodotoluene with Magnesium and Lithium.*

By ROY C. HINTON, FREDERICK G. MANN, and IAN T. MILLAR.

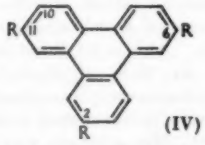
The reaction of 3-bromo-4-iodotoluene with magnesium and lithium has been studied with particular reference to the neutral products. The action of magnesium gives a crude product which contains 2 : 6-dimethyldiphenylene and on carboxylation affords 2 : 7-dimethylfluorenone. The product from the action of lithium contains 2 : 6 : 11-trimethyltriphenylene, and on hydrolysis also furnishes 4 : 4′-dimethyldiphenyl.

The probable mechanisms by which these compounds are formed are discussed.

MAGNESIUM reacts with *o*-di-iodobenzene,[1] *o*-bromoiodobenzene,[2] and 3-bromo-4-iodotoluene[3] (I) to give diphenyl, diphenylene (II; R = H), and 2 : 6-dimethyldiphenylene (II; R = Me) respectively, in addition to other products in each case. Diphenyl is also undoubtedly formed in this reaction with *o*-bromoiodobenzene, but it co-distils with diphenylene, and consequently in the above experiments the reaction product was treated with carbon dioxide, whereby fluorenone (III; R = H) was formed and was readily separated from the diphenylene. Lithium reacts with *o*-di-iodobenzene and *o*-bromoiodobenzene to give triphenylene (IV; R = H). The probable mechanisms of the reactions producing these compounds, particularly those from *o*-bromoiodobenzene, have been discussed.[2,3]



(I) (II) (III)



(IV)

We now record a brief investigation of the neutral compounds formed by the action of these metals on 3-bromo-4-iodotoluene (I), particularly as in the earlier experiments 2 : 6-dimethyldiphenylene (II; R = Me) arose incidentally in the synthesis of 4-methyl-*o*-phenylenebis(diethylphosphine)[3] and consequently was initially highly impure: the action of carbon dioxide on the crude reaction mixtures has not been studied except as an aid to the isolation of the neutral products.

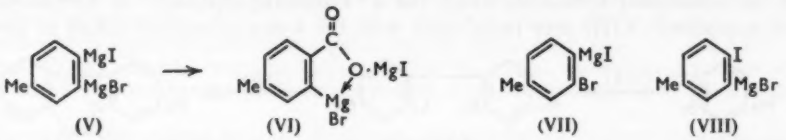
When 3-bromo-4-iodotoluene (I) was brought into reaction with magnesium in ether, initially with cooling and finally with boiling under reflux, and the chilled product then carboxylated, the usual working up gave a neutral fraction which furnished 2 : 6-dimethyldiphenylene (II; R = Me) and 2 : 7-dimethylfluorenone (III; R = Me).

The acidic fraction furnished *p*-toluic acid, 2-bromo-4-methylbenzoic acid, a trace of 2-iodo-5-methylbenzoic acid, and a gummy residue the components of which could not be satisfactorily isolated but which were almost certainly substituted diphenic acids.

[1] Heaney, Mann, and Millar, *J.*, 1956, 1.
[2] *Idem*, *J.*, 1957, 3930.
[3] Hart and Mann, *J.*, 1957, 3939.

XUM

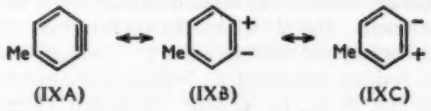
The formation of these three identified acids shows that the magnesium has reacted with 3-bromo-4-iodotoluene (I) to give the di-Grignard reagent (V), and the mono-Grignard

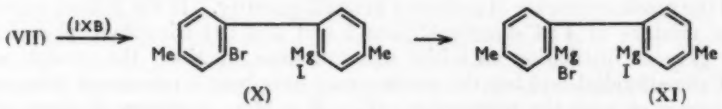


reagents (VII) and (VIII), the last however in very small proportion. The formation of the di-Grignard reagent (V) has already been proved by its conversion into the above diphosphine:[3] complete carboxylation of this reagent is undoubtedly prevented by the formation of the comparatively stable chelated intermediate (VI),[1] which on hydrolysis furnishes the *p*-toluic acid.

3-Bromo-4-iodotoluene (I) reacted with lithium in cold ether to give 2 : 6 : 11-trimethyltriphenylene (IV; R = Me), m. p. 128·5—129·5° after purification by conversion into its orange picrate, m. p. 191—192°, and also, after hydrolysis of the crude reaction mixture, 4 : 4′-dimethyldiphenyl. The identity of the hydrocarbon (IV; R = Me) is based on the following evidence. (*a*) Analysis, molecular-weight determination, and its absorption spectrum show the hydrocarbon to be a trimethyltriphenyl. (*b*) The only other isomer having one methyl group substituted in each benzene ring in other than the *ortho* positions is 2 : 6 : 10-trimethyltriphenylene, which Barker, Emmerson, and Periam [4] have prepared by an unambiguous synthesis and which has m. p. 190° and gives an orange picrate, m. p. 221—222°. We are greatly indebted to Dr. C. C. Barker for a specimen of this hydrocarbon for comparison with our 2 : 7 : 10-isomer.

The formation of these neutral compounds by the action of magnesium and lithium is of great interest and provides strong support for the mechanisms suggested for the reactions of *o*-bromoiodobenzene with these metals.[2] It is clear that the reagent (VII) is the chief mononuclear Grignard reagent formed, and that it could, by loss of magnesium dihalide, generate in solution the highly reactive transient 4-methylbenzyne, of which (IXA, B,





and C) are canononical forms. The dimerisation of either of the polar forms (IXB) or (IXC)—originally suggested by Lüttringhaus and Schubert [5] for benzyne itself—would give 2 : 6-dimethyldiphenylene (II; R = Me), and only a cross-dimerisation of (IXB) and (IXC) would provide the 2 : 7-isomer. The product obtained in our present experiments was readily purified, and no indication of an isomer could be obtained.

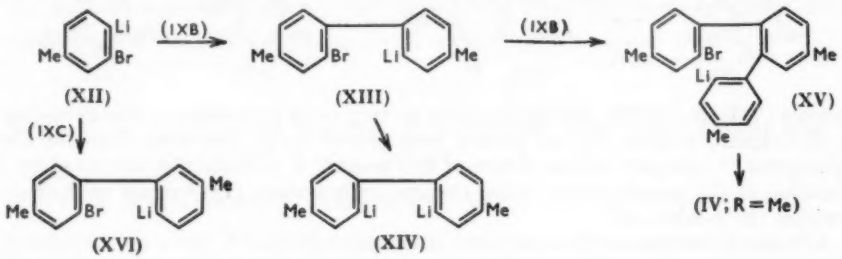
The interaction of the 4-methylbenzyne (IXB) with the ionised Grignard reagent (VII) would give the diphenyl derivative (X), which could then react with more magnesium to give the di-Grignard reagent (XI): carboxylation of this reagent (XI) would give 2 : 7-dimethylfluorenone (III; R = Me).

It is noteworthy that a similar interaction of the 4-methylbenzyne (IXC) with the reagent (VII) would have given 2 : 6-dimethylfluorenone, which was not detected.

A similar selective action apparently operates with the lithio-derivatives. Reaction

[4] Barker, Emmerson, and Periam, *J.*, 1958, 1077.
[5] Lüttringhaus and Schubert, *Naturwiss.*, 1955, **42**, 17.

of the lithio-derivative (XII) with the 4-methylbenzyne (IXB) will give the lithiodiphenyl derivative (XIII). A portion of this compound may undergo further lithiation to (XIV) which on subsequent hydrolysis forms the 4 : 4′-dimethyldiphenyl. A further portion of this compound (XIII) may react again with the 4-methylbenzyne (IXB) to give the



lithio-derivative (XV), which by loss of lithium bromide forms 2 : 6 : 11-trimethyltriphenylene (IV; R = Me): the latter would also be formed if the compound (XIII) reacted similarly with the 4-methylbenzyne (IXC).

It is noteworthy that if the initial reaction of the lithio-derivative (XII) occurred with the 4-methylbenzyne (IXC), the product (XVI) on further lithiation and hydrolysis would furnish 3 : 4′-dimethyldiphenyl: furthermore, this product (XVI), if it reacted again with the 4-methylbenzyne (IXC) would give 2 : 6 : 10-trimethyltriphenylene, but reaction with the 4-methylbenzyne (IXB) would furnish the 2 : 6 : 11-isomer.

Although there can be little doubt regarding the general mechanism by which the above neutral products are formed, decisive evidence for the specifically selective initial operation of the 4-methylbenzyne in the form (IXB), which is necessary for the production of the compounds (III; R = Me), (IV; R = Me), and 4 : 4′-dimethyldiphenyl, is dependent on the absence of isomers of each of these compounds. The probability that isomeric forms were discarded during the separation and purification of the components of the crude mixtures, which were always obtained in small quantity, must be assessed.

In the magnesium experiments, the 2 : 6-dimethyldiphenylene (II; R = Me) was readily purified by steam-distillation, and therefore the 2 : 7-isomer, which is also volatile in steam,[6] was absent. The residue furnished 2 : 7-dimethylfluorenone (III; R = Me) on recrystallisation, but the rise in m. p. without significant change in composition indicated the possible presence of an isomer in small quantity. In the lithium experiments, the crude mixture of 4 : 4′-dimethyldiphenyl and 2 : 6 : 11-trimethyltriphenylene (IV; R = Me) gave on distillation an initial semicrystalline fraction: the crystals were the pure 4 : 4′-dimethyldiphenyl but the fraction may have been a mixture of this compound with an isomer or with the triphenylene (IV; R = Me). Addition of picric acid to a solution of the undistilled residue deposited the almost pure picrate of 2 : 6 : 11-trimethyltriphenylene: the picrate of the 2 : 6 : 10-isomer has a closely similar solubility, and this hydrocarbon was almost certainly absent. The evidence indicates therefore that initial reaction of the 4-methylbenzyne (IXB) with the reagents (VII) and (XII) must constitute the dominant, if not the exclusive, reaction of the methylbenzyne in these series of changes.

Experimental

Reaction with Magnesium.—A solution of 3-bromo-4-iodotoluene (I) (93 g.) in ether (250 c.c.) was added dropwise with stirring to magnesium (18 g., 2·2 atomic equivalents) in a nitrogen atmosphere, the reaction being initially controlled by ice-cooling. The complete mixture was boiled under reflux for 3 hr., cooled, and filtered directly on to crushed solid carbon dioxide (1 kg.), leaving unchanged magnesium (7·8 g., 0·9 atomic equivalent). The mixed product was allowed to attain room temperature, and was then hydrolysed with dilute sulphuric acid and

[6] Lothrop, *J. Amer. Chem. Soc.*, 1941, **63**, 1187.

XUM

thoroughly extracted with ether. The united ethereal extracts were extracted with 10% aqueous sodium hydroxide.

Evaporation of the ethereal solution gave a brown liquid, from which steam-distillation gave 2 : 6-dimethyldiphenylene (II; R = Me) as a yellow distillate which solidified, and from aqueous ethanol furnished pale yellow crystals (0·12 g., 0·4%), m. p. 138—140° (lit.,[3] 139—141°) (Found: C, 93·1; H, 6·6. Calc. for $C_{14}H_{12}$: C, 93·3; H, 6·7%). A benzene or toluene solution when mixed with methanolic picric acid deposited a red crystalline picrate, too unstable for isolation.

The brown solid residue from the distillation, when twice recrystallised from ethanol, gave bright yellow 2 : 7-dimethylfluorenone (III; R = Me), m. p. 142—145° (Found: C, 86·4; H, 6·1. Calc. for $C_{15}H_{12}O$: C, 86·5; H, 5·8%), and after a third recrystallisation (0·3 g., 0·9%) m. p. 150—151° (lit.,[7] m. p. 157°) (Found: C, 86·7; H, 6·2%): it gave a red 2 : 4-*dinitrophenylhydrazone*, m. p. 259—260° (decomp.) (from dioxan) (Found: C, 65·0; H, 4·4; N, 14·5. $C_{21}H_{16}O_4N_4$ requires C, 64·9; H, 4·2; N, 14·4%). The nuclear magnetic resonance spectrum of the fluorenone (III; R = Me) gave strong evidence for a symmetrical distribution of the methyl groups. The only other symmetric isomer which could have been formed is 3 : 6-dimethylfluorenone, which has m. p. 118°.[8]

The sodium hydroxide extract gave, on acidification, a gum which could not be readily recrystallised. It was therefore treated in ethereal solution with an excess of diazomethane; the mixture of methyl esters on distillation gave the fractions, (1) b. p. 100—112°/15 mm. (2·9 g.), (2) b. p. 112—175°/15 mm. (8·7 g.), and (3) 97—215°/0·2 mm. (8·0 g.). Fraction (1) was methyl *p*-toluate (Found: C, 72·1; H, 6·9. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·7%); hydrolysis gave *p*-toluic acid, m. p. 177—179° (lit.,[9] 179°), characterised as its anilide, m. p. 144—145° (lit.,[10] 144—145°) (Found: C, 79·3; H, 6·6; N, 6·8. Calc. for $C_{14}H_{13}ON$: C, 79·6; H, 6·1; N, 6·6%), with unchanged mixed m. p.s for each compound.

Fraction (2) on redistillation gave (*a*) a major fraction, b. p. 152—159°/15 mm. (7·1 g.), and (*b*) a very small higher fraction, b. p. 95—195°/0·1 mm. Fraction (*a*) was methyl 2-bromo-4-methylbenzoate (Found: C, 46·8; H, 4·2. Calc. for $C_9H_9O_2Br$: C, 47·2; H, 4·0%): aqueous alkaline hydrolysis furnished the acid, from which traces of *p*-toluic acid were removed by steam-distillation, but repeated recrystallisation from light petroleum (b. p. 60—80°) was required to obtain the pure 2-bromo-4-methylbenzoic acid, m. p. 138·5—139·5° (lit.,[11] 140°) (Found: C, 44·6; H, 3·2. Calc. for $C_8H_7O_2Br$: C, 44·7; H, 3·3%). Fraction (*b*) on distillation gave a fraction, b. p. 110—156°/0·5 mm., which on hydrolysis furnished undoubtedly 2-iodo-5-methylbenzoic acid, m. p. 126·5—129° after repeated recrystallisation as before from light petroleum—it was still contaminated with the previous acid (Found: C, 37·4; H, 2·9. Calc. for $C_8H_7O_2I$: C, 36·7; H, 2·7%).

Reaction with Lithium.—A solution of 3-bromo-4-iodotoluene (15·4 g.) in ether (80 c.c.) was added dropwise to a stirred mixture of fine lithium foil (1·7 g., 4·6 atomic equivalents) in ether (80 c.c.) under nitrogen, a moderate reaction occurring after *ca.* 15 min. Benzene (100 c.c.) was then added and the mixture stirred at room temperature for 3 hr., cooled, and filtered on to crushed ice: unchanged lithium (0·9 g., 2·4 equivalents) was collected. The organic layer was separated, and on removal of the ether afforded a brown oil consisting of 4 : 4′-dimethyldiphenyl and 2 : 6 : 11-trimethyltriphenylene (IV; R = Me). A reasonably sharp separation of these components by distillation was not possible, because although the diphenyl began to distil first, co-distillation of the two components steadily increased. An early and incomplete fraction of 4 : 4′-dimethyldiphenyl was collected at 80—140°/0·3 mm., and formed a semi-crystalline mass: the crystals, when sublimed or recrystallised from ethanol gave the pure compound (Found: C, 91·9; H, 8·0. Calc. for $C_{14}H_{14}$: C, 92·25; H, 7·7%), m. p. 118·5—120°, unaffected by admixture with an authentic sample (lit.,[12] 122°).

The residue, in ether, was passed through an alumina column, the ether then removed, and the residue extracted with boiling ethanol. A benzene solution of the final residue, when treated with ethanolic picric acid, deposited 2 : 6 : 11-*trimethyltriphenylene picrate*, which, on

[7] Bergmann, Berthier, Hirschberg, Loewenthal, Pullman, and Pullman, *Bull. Soc. chim. France*, 1951, 669.
[8] Chardonnens and Würmli, *Helv. Chim. Acta*, 1946, **29**, 922.
[9] Gattermann, *Annalen*, 1888, **244**, 51.
[10] Hantzsch, *Ber.*, 1891, **24**, 58.
[11] Claus, *J. prakt. Chem.*, 1889, **39**, 486.
[12] Ullmann and Meyer, *Annalen*, 1904, **332**, 44.

XUM

crystallisation from ethanol containing a small proportion of benzene, gave orange crystals (0·95 g., 11%), m. p. 191—192° (decomp.) (Found: C, 65·3; H, 4·3; N, 8·3. $C_{21}H_{18},C_6H_3O_7N_3$ requires C, 64·9; H, 4·2; N, 8·4%). The picrate when added to boiling water deposited very pale brown 2 : 6 : 11-*trimethyltriphenylene*, m. p. 128·5—129·5° [from light petroleum (b. p. 60—80°)] (Found: C, 93·4; H, 6·8%; *M*, in freezing benzene, 268. $C_{21}H_{18}$ requires C, 93·3; H, 6·7%; *M*, 270·4). It deposited a yellow 1 : 3 : 5-trinitrobenzene addition product, m. p. 219—222° (decomp.), from benzene solution.

The experimental data regarding 2 : 6 : 10-trimethyltriphenylene were omitted by an oversight in ref. 4, but Dr. C. C. Barker states in a personal communication: " Self-condensation of 4-methyl*cyclo*hexanone gave the sparingly soluble dodecahydro-2 : 6 : 10-trimethyltriphenylene, m. p. 195°, and this compound was readily dehydrogenated with palladium–charcoal to give 2 : 6 : 10-*trimethyltriphenylene*, m. p. 190° (Found: C, 93·3; H, 6·7. $C_{21}H_{18}$ requires C, 93·3; H, 6·7%)." This hydrocarbon gave an orange *picrate*, m. p. 221—222°, prepared and recrystallised as the former picrate (Found: C, 64·6; H, 4·3; N, 8·5. $C_{21}H_{18},C_6H_3O_7N_3$ requires C, 64·9; H, 4·2; N, 8·4%).

(A) $\lambda_{max.}$ (mμ)	254	263	278	289	333	340	349
$\log_{10}\varepsilon$	4·95	5·20	4·32	4·25	2·93	2·72	2·81
(B) $\lambda_{max.}$ (mμ)	249	258	273	285	315	327	333
$\log_{10}\varepsilon$	4·95	5·2	4·3	4·25	3·2	3·0	3·15
(C) $\lambda_{max.}$ (mμ)	253·5	262·5	277·5	288·5			
$\log_{10}\varepsilon$	4·94	5·18	4·30	4·23			

The annexed Table gives the ultraviolet absorption spectra, in 95% ethanol, of (A) 2 : 6 : 11-trimethyltriphenylene, (B) triphenylene, for which Heaney, Mann, and Millar's values [1] are given, (C) 2 : 6 : 10-trimethyltriphenylene, these being the only values given by Barker *et al.*[4]

In a similar experiment, the reaction mixture was carboxylated, but no acidic products were isolated; the crude neutral components were not examined in detail, but in solution gave 2 : 7-dimethylfluorenone 2 : 4-dinitrophenylhydrazone (1·4%), m. p. and mixed m. p. 256—257° (from dioxan).

We gratefully acknowledge a grant (to R. C. H.) provided by Imperial Chemical Industries Limited, Dyestuffs Division.

University Chemical Laboratory, Cambridge.
University College of North Staffordshire,
Keele, Staffordshire.

[*Received, July 22nd,* 1958.]

---

949. *Condensed Ions in Aqueous Solution. Part I. Ion-exchange Behaviour of Vanadate Ions.*

By R. U. Russell and J. E. Salmon.

The ionic species formed during condensation of vanadate ions in solution as the pH is lowered are subject to ionic-sieve effects in exchange reactions with anion-exchangers of the DeAcidite F.F. type. By means of this effect and by the use of resins of various weight-swellings, evidence has been obtained for the existence of di-, tri-, tetra-, hexa-, and deca-vanadate ions at different stages in the condensation.

Early studies of the vanadates were concerned primarily with the nature of the solid compounds which separated from solution,[1] but both Roscoe [2] and Rammelsberg [3] indicated that these materials were of increasing complexity as the acidity of the solutions was increased.

The first systematic studies of the nature of the species present in solution were those

[1] Mellor, " Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, Green and Co., London, 1935, Vol. IX, p. 757.
[2] Roscoe, *Phil. Trans.*, 1868, **158**, 1; 1869, **159**, 679; 1870, **160**, 317.
[3] Rammelsberg, *Pogg. Annalen*, 1856, **98**, 249; *Wied. Annalen*, 1883, **20**, 928.

by Düllberg [4] who showed by cryoscopic measurements that ions containing three and six vanadium atoms were among those formed. This and subsequent work indicated possible stages in the condensation to be ortho-, pyro- (di-), meta- (probably tri-), tetra-, penta-, hexa-, octa-, and deca-vanadate.

Evidence for the existence of ortho- and pyro-vanadate ions in alkaline solutions has been provided by diffusion (Jander and Jahr [5]), dialysis (Brintzinger and Wallach [6]), potentiometric titration (Britton and Robinson;[7] Britton and Welford [8]), and by the work of Souchay and his collaborators.[9]

There appears to be general agreement that the next stage of condensation after pyrovanadate, corresponds to a metavanadate ion and that this occurs at about the neutral point. Düllberg,[4] Brintzinger and Wallach,[6] and Souchay and his co-workers [9] all concluded that this ion contains three vanadium atoms.

Evidence for a tetravanadate ion has been found by Jander and Jahr,[5] Brintzinger and Wallach,[6] and Trujillo and Tejera,[10] of whom the last named based their conclusions on solubility measurements. The formation of a pentavanadate ion, however, has been reported only by Jander and Jahr [5] and by Britton and Welford.[8] Since the last workers merely gave an empirical formula and since this ion was found in solutions of low pH it is probably a decavanadate.

The presence, in acid solutions, of hexavanadate ions has been reported by Düllberg,[4] Souchay,[9] Martinez and Trujillo,[11] and Ducret,[12] but was doubted by Britton and Welford [8] and by Jander and Jahr [5] who, however, found evidence of an unstable octavanadate.

Ducret [12] was of the opinion that an ion larger than the hexavanadate ion was formed in more strongly acid solutions and the empirical formula assigned by Britton and Welford to the most highly condensed ion which they detected could correspond to a decavanadate. The existence of such an ion was confirmed by Rossotti and Rossotti.[13]

The diversity of the reports together with the lack of knowledge of the pH ranges over which the various stages of condensation occurred indicated a need for further study. The ion-exchange techniques which proved useful for similar cases [14] have again been used.

Experimental

Preparation of Solutions.—Vanadic acid solutions (*ca.* 0·05 g.-atom of vanadium per l.; pH 2—2·1) were prepared by passage of solutions of analytical-grade ammonium vanadate (2 l., *ca.* 0·06 g.-atom of vanadium per l.) through a column of ZeoKarb 225 (H^+ form; 20 cm. long, 4 cm. in diameter). Part of the vanadium was sorbed on the resin as a dark band below the ammonium band and above the hydrogen band. This dark band consisted of quinquevalent (yellow) and quadrivalent (blue) species, of which the former were easily removed by washing, but the latter were displaced only on treatment with acid. No quadrivalent vanadium was present in the vanadic acid. The amount of reduced material present on the column decreased with use but was finite, even after many cycles (cf. Salmon and Tietze [15]). Vanadic acid solutions thus prepared were stable for several days after which precipitation might occur. The column was regenerated with 2N-acid and washed free from regenerant before re-use.

Vanadate solutions of higher pH were obtained, either by mixing vanadic acid and ammonium vanadate solutions or, more conveniently, by the addition of ammonia solution (*d* 0·880) to

[4] Düllberg, *Z. phys. Chem.*, 1903, **45**, 129.
[5] Jander and Jahr, *Z. anorg. Chem.*, 1933, **211**, 49; 1933, **212**, 1; 1934, **220**, 201.
[6] Brintzinger and Wallach, *ibid.*, 1934, **224**, 103.
[7] Britton and Robinson, *J.*, 1933, 512.
[8] Britton and Welford, *J.*, 1940, 764.
[9] Carpeni and Souchay, *J. Chim. Phys.*, 1945, **42**, 149; *Bull. Soc. chim. France*, 1946, **13**, 160; Souchay, *ibid.*, 1951, **18**, 932; Souchay and Chauveau, *Compt. rend.*, 1957, **244**, 1923.
[10] Trujillo and Tejera, *Anal. Fis. Quim.*, 1954, **50**, *B*, 399.
[11] Martinez and Trujillo, *ibid.*, 1949, **45**, *B*, 719; 1950, **46**, *B*, 639; 1951, **47**, *B*, 699.
[12] Ducret, *Ann. Chim.* (*France*), 1951, **6**, 705.
[13] Rossotti and Rossotti, *Acta Chem. Scand.*, 1956, **10**, 457.
[14] (*a*) Everest and Salmon, *J.*, 1954, 2438; (*b*) *J.*, 1955, 1444; Everest and Popiel, *J.*, 1956, 3183; *J.*, 1957, 2433; *J. Inorg. Nucl. Chem.*, 1958, **6**, 153.
[15] Salmon and Tietze, *J.*, 1952, 2324.

XUM

vanadic acid. In either case the mixed solutions were left before use for periods varying from several hours (pH <5 or >8) to several days (pH 5—8), to permit equilibrium to be reached.

Anion-exchange Resins.—The anion-exchangers used were the strongly basic DeAcidite F.F. resins, air-dried in the chloride form, in varying degrees of cross-linking, and similar laboratory prepared resins made according to the method of Pepper, Paisley, and Young.[16] The chloride form of a resin, as received, was treated with 2N-hydrochloric acid, washed with water, and allowed to dry in air. All the resins used had capacities of the order of 3·8 milliequivs./g. of air-dried resin and experience showed that the effective pore sizes of these resins in a given solution were in direct relation to their weight-swelling values, regardless of any differences in method of preparation. These values, which provide a measure of the swelling which occurs when a dry resin is placed in water, were measured by the method of Pepper *et al.*[16]

Batch Experiments.—Two procedures were used. In the first 0·5 g. of resin was left in contact with 75 ml. of vanadic acid–ammonium vanadate solution, of known pH and vanadium content, for known times at room temperature, with occasional swirling. The resin and the aqueous phase were separated by filtration through a small glass column (*ca.* 1 cm. in diameter and 8 cm. in length), with a sintered disc (porosity grade 2, sealed in), and aliquot parts of the filtrate analysed for vanadium and used for pH measurement. The chloride on the resin was then removed and was determined by a method given previously,[14a] as was the capacity of the resin.

In the second procedure 0·5 g. of resin (or less, where specified) was left in contact with 100 ml. of solution under the above conditions. The two phases were separated by decantation and aliquot parts of the aqueous phase used for the determination of vanadium, chloride, and pH.

The R value, as defined by Everest and Salmon,[14a] which expresses the ratio of the mean number of vanadium atoms per unit of ionic charge in the vanadate ions sorbed on the resin, was then derived as follows:

In the first case;

$$R = \frac{\text{G.-atoms of V in soln. initially} - \text{g.-atoms of V in soln. finally}}{\text{Capacity of resin sample} - \text{g.-atoms of Cl on resin finally}}$$

where the resin capacity is given in g.-equivs.

In the second case

$$R = \frac{\text{G.-atoms of V in soln. initially} - \text{g.-atoms of V in soln. finally}}{\text{G.-atoms of Cl in soln. finally}}$$

which expression does not involve the value of resin capacity.

Column Experiments.—A volume of solution containing more vanadium than was required to saturate the exchanger with vanadium (by a factor of several-fold) was passed through a column (1 × 8 cm.) containing 1 g. of resin during 2 days. The effluent was then free from chloride, and vanadate ions only were sorbed on the resin. The resin was washed thoroughly, the vanadate ions were then displaced by use of 2N-sulphuric acid, and vanadium was determined in the effluent. For the experiments R was given by the ratio (g.-atoms of V sorbed on resin)/(capacity of resin sample in g.-equivs.).

Analysis.—Vanadium was determined, after reduction to the quadrivalent state with sulphur dioxide or preferably sodium sulphite, by titration with potassium permanganate solution. Elimination of interference by chloride in the solutions could be achieved by evaporation of the V^{IV} solutions to small bulk (not to dryness) in the presence of 3N-sulphuric acid, followed by dilution before titration.

Chloride was determined by weight as silver chloride. pH measurements were made with a Cambridge pH meter with a glass–saturated calomel electrode system.

pH *Titrations.*—The procedure used was similar to that of Ducret;[12] vanadic acid was titrated with ammonia solution, and the pH was measured immediately after mixing and again after the solution had reached equilibrium.

Spectrophotometric Measurements.—These were made with 1 cm. quartz cells and a Unicam S.P. 500 spectrophotometer with solutions of 0·025 g.-atom of vanadium per litre.

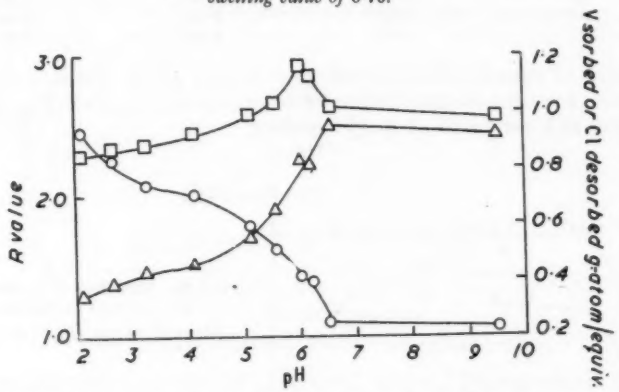
[16] Pepper, Paisley, and Young, *J.*, 1953, 4097.

Results and Discussion

In experiments with vanadic acid solutions (pH 2, *ca.* 0·05 g.-atom/l.), carried out within the time limits of their stability and with resin of a normal degree of cross linking (weight-swelling 0·70), no consistent changes in the value of R with time could be detected, where R is the ratio of the mean number of vanadium atoms to ionic charge (x/z) in the vanadate ions $(H_wV_xO_y)^{z-}$ sorbed by the resin.[14a]

Studies made with the same resin, but with solutions of varying pH (Fig. 1), and with times of contact of up to 100 hr. showed that, whilst the value of R increased with decrease in pH, the corresponding values of vanadium sorption and chloride release—from which R is derived—increased with rise in pH, but reached a maximum value at pH *ca.* 6·5, above which the chloride release remained constant while the vanadium uptake decreased.

Fig. 1. *Experiments with vanadate solutions (75 ml.) of various* pH *values and a resin of weight-swelling value of* 0·70.



G.-atoms of V sorbed per equiv. of resin (□), g.-equiv. of Cl desorbed per equiv. of resin (△), R value (○).

Such behaviour can be explained by the assumption that larger ions (*i.e.*, with higher R values) are formed in increasing amounts as the pH is lowered, but are excluded, at least partially, by the resin structure.

If such an ionic-sieve mechanism is effective, the maximum in the vanadium sorption curve should correspond to the sorption of the largest ions which can penetrate the resin structure without hindrance. Larger ions, formed in maximum concentration at lower pH, are not sorbed owing to their size and low concentration, whilst smaller ions are not sorbed owing to their relatively lower affinity for the resin and their low concentration. The mean value of $R = 1{\cdot}33$ at this peak in vanadium sorption would then indicate the sorption of a tetravanadate ion ($x = 4$, $z = 3$).

Support for the view that exclusion was occurring with the resin of weight-swelling value 0·70 was provided by the results of similar experiments with resins of other weight-swelling values.

Thus in experiments with a more open resin (weight-swelling 1·04) the peak in vanadium sorption was replaced by a steady rise in sorption with fall in pH while the value of R rose to above three at about pH 2. With a more tightly cross-linked resin, on the other hand, a maximum in vanadium sorption occurred but at a higher pH (*ca.* 7), and this corresponded to an ion with an R value of unity.

With a resin of weight-swelling value 0·74 it was observed that the value of R remained close to 2 over the pH range 4·5—6, which again corresponded to a maximum in the sorption of vanadium.

XUM

In the sorption of ions comparable in size with the effective pore size of the resin, slow rates of exchange were encountered. The results obtained with resin of weight-swelling value 1·04 and vanadic acid are shown in Table 1 which shows a steady state after 100 hr., and the values of R corresponding to this state are those included in subsequent graphs and Tables.

TABLE 1. *The variation of exchange with time, with vanadic acid* (100 *ml.*, pH *ca.* 2) *and* 0·5 *g. of resin* (1·04 *weight-swelling*).

Time (hr.)	Cl desorbed (mg. equiv.)	V sorbed (mg.-atom)	R
5	0·754	1·926	2·56
10	0·781	2·022	2·59
25	0·892	2·384	2·67
50	0·995	2·795	2·90
60	1·020	2·978	2·97
80	1·013	2·949	2·91
90	1·038	3·048	2·94
100	1·017	2·986	2·94

For solutions of vanadic acid (*ca.* 0·05 g.-atom/l. at pH 2), the sorption of an ion of R 3·3 by resins of weight-swelling about 1·4 or greater is indicated (Fig. 2) with partial exclusion of this at lower values of weight swelling.

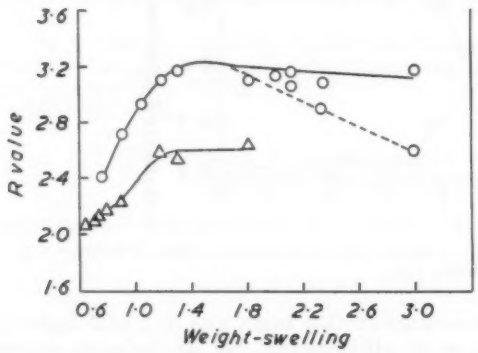


FIG. 2. *Variation of R with weight-swelling for solutions in the low* pH *range.*
Mean R values at pH 2 (○) and 4 (△).

A value of $R = 3·33$ is consistent with the sorption of a decavanadate ion ($x = 10$, $z = 3$). The fact that this ion has a large affinity for the resin, coupled with the presence in it of ten vanadium atoms, leads to a high removal of vanadium from solution (in some cases 75%), with the possible consequence of an increase in the charge on the decavanadate ion (if it is capable of losing more protons) and a tendency for a reversal of the condensation to yield smaller ions. A decrease in R value with increased weight-swelling, as observed (Fig. 2 broken curve), could arise from either of these causes. If the decrease in vanadium concentration is kept below 50% by the use of 0·25 g. quantities of resin this decrease in

TABLE 2. *Values of R obtained with vanadic acid* (100 *ml.*) *and* 0·25 *g. samples of resins of high weight-swelling values.*

Weight-swelling	R values					Mean R value
7·4	3·21	3·44	3·34	3·23	3·49	3·34
17·5	3·13	3·23	3·23	3·26	3·14	3·20

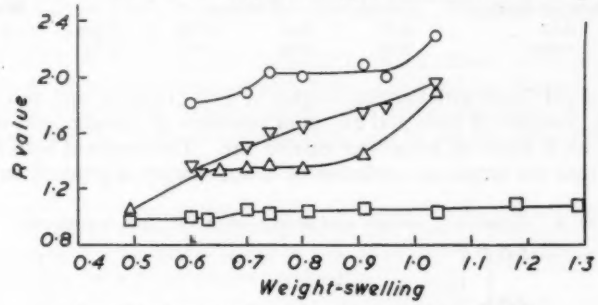
R is minimized (Fig. 2, full curve). No higher R values were detected with resin of weight-swelling values up to 17 and a maximum value of 3·33 was confirmed (Table 2).

With similar solutions, but at pH 4 (Fig. 2), the sorption of an ion having an R value close to 2 was observed with resins of weight-swelling below 0·75, but increasing amounts of a larger ion, presumably the decavanadate, were sorbed by more open resins. An ion

with an R value of 2 was sorbed from solutions of pH 5 (Fig. 3) over a range of weight-swelling, indicating the presence of such an ion in solution in significant concentrations, together with small amounts of smaller ions, which were sorbed when the ion present in major proportion was excluded at low weight-swellings, and of larger ions which were sorbed with it by more open resins. At pH 6·5 (Fig. 3), however, a smaller ion having an R value of 1·33 was evidently in preponderance, probably together with ions of $R = 1$ and larger ions of $R = 2$. Results obtained with solutions of pH 6 (Fig. 3) also indicated the presence of an ion of $R = 1{\cdot}33$, but in smaller amounts together with that of $R = 2$. The R values rise steadily from the lower weight-swelling value 0·6 to the higher value 1·05.

Evidently at pH 6·5 the tetravanadate ions ($x = 4$, $z = 3$) are present in solution as the predominant species, but as the pH is lowered, even to pH 6, they give way increasingly to the ion of $R = 2$. A value of $R = 2$ would correspond to a hexavanadate ($x = 6$, $z = 3$) or an octavanadate ($x = 8$, $z = 4$) ion, but a consideration of the weight-swelling values

FIG. 3. *The variation of R with weight-swelling for solutions in the middle* pH *range.*



Mean R values at pH 5 (○), 6 (▽), 6·5 (△), and 7 (□).

which will permit free entry of ions of R values 3·33, 2, and 1·33 respectively (Figs. 2 and 3; Table 3) shows that the ion of $R=2$ is much closer in size to the tetravanadate than to the decavanadate and is, therefore, presumably a hexavanadate.

At pH 7 (Fig. 3), the formation of an ion of $R=1$ in appreciable concentration was apparent. That this was a trivanadate ion ($x = 3$, $z = 3$) was shown by the fact that it was capable of entering resins of only slightly lower weight-swellings than those which permitted the entry of tetravanadate ions (Table 3). This conclusion was supported by the

TABLE 3. *Approximate minimum weight-swelling values of resins which just permit the entry of various vanadate ions* $H_wV_xO_y^{z-}$.

R value	3·33	2·00	1·33	1·00
x (estimated)	10	6	4	3
Weight-swelling	1·40	0·75	0·65	0·60

TABLE 4. *R values obtained from experiments with vanadate solutions at* pH 10.

Weight-swelling	R values					Mean R value
0·70	0·77	0·77	0·77	0·78	0·77	0·77
0·63	0·80	0·83	0·85	0·84	0·84	0·83
0·60	0·77	0·78	0·78	0·77	0·81	0·78
0·49	0·68	0·69	0·70	0·69	0·68	0·69

fall of R below 1 for the most tightly cross-linked resins (Fig. 3), by the exchange reactions of these resins with solutions of higher pH (Table 4) in which R values of about 0·66 [corresponding to the divanadate ion ($x = 2$, $z = 3$)] or slightly higher, were obtained. An indication was thus obtained that ions existed in alkaline solution which were smaller than those of $R = 1$ and since these appeared to contain two vanadium atoms ($x = 2$, $z = 3$), the value of $R = 1$ would correspond to a trivanadate ion.

XUM

To ascertain the effects of changes in the vanadium concentration, which occurred during the ion-exchange process, on the nature of the ions in solution, batch experiments

TABLE 5. *The variation of R value with change of vanadate concentration at* pH 7.

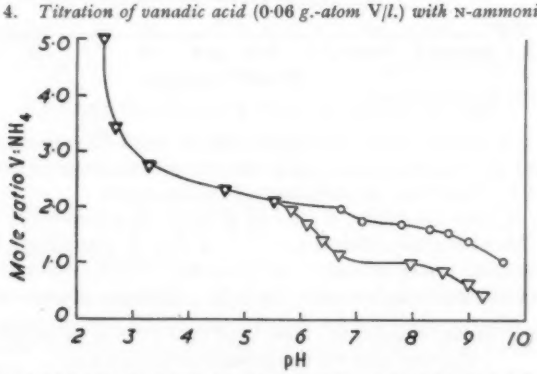
Solutions: V concn. (g.-atom/l.)	Resins Sample (g.)	Weight-swelling	Mean *R*	Solutions: V concn. (g.-atom/l.)	Resins Sample (g.)	Weight-swelling	Mean *R*
0·14	0·5	1·04	1·12	0·035	0·2	1·04	0·96
0·14	0·5	0·91	1·14	0·035	0·2	0·91	0·99
0·14	0·5	0·74	1·15	0·035	0·2	0·74	1·03
0·07	0·3	1·04	1·01				
0·07	0·3	0·91	1·02				
0·07	0·3	0·74	1·13				

TABLE 6. *Column experiments with vanadic acid solutions and a resin of weight-swelling value* 1·82.

V concn. (g.-atom/l.)	*R* values				Mean *R*
0·05	3·27	3·41	3·31	3·30	3·32
0·005	2·80	2·84	2·81	2·83	2·82

with solutions of pH 7 and with varying weights of resin (Table 5), and also column experiments with 1 g. samples of resin and excess of solutions of vanadic acid of varying concentration (pH *ca.* 2, Table 6), have been carried out. The results of both series of experiments showed that the degree of condensation is not sharply dependent on concentration

FIG. 4. *Titration of vanadic acid* (0·06 *g.-atom* V/*l.*) *with* N-*ammonia.*



pH values: initial (○), final (▽), identical initial and final (circle inside triangle).

and hence that the results of the batch experiments given in Figs. 2 and 3 would indicate reliably the species present in solution at the various pH values.

The observed fall in *R* of vanadic acid solutions with dilution (Table 6) could be due to increased ionisation of the acid (to $x = 10$, $z = 4$, $R = 2{\cdot}5$) which would be consistent with the observations of Rossotti and Rossotti.[13] Thus, whilst it is not possible to maintain a constant ionic strength in the aqueous phase in these experiments our conclusions are not seriously affected by changes in concentration during the ion-exchange process, with the one exception already noted (Fig. 2), where this was overcome by modifying the procedure.

The present results thus indicate the following sequence of condensation: at pH 10 divanadate ($x = 2$, $z = 3$); at pH 7 trivanadate ($x = 3$, $z = 3$); at pH 6·5 tetravanadate ($x = 4$, $z = 3$); at pH 5 hexavanadate ($x = 6$, $z = 3$); at pH 2 decavanadate ($x = 10$, $z = 3$), and possibly at lower concentration ($x = 10$, $z = 4$). Of these ions the trivanadate,

hexavanadate, and decavanadate appear to persist over a wide pH range, while the tetravanadate exists over a narrow range only.

The greater stability of the hexavanadate and trivanadate ions seems to be shown by the appearance of inflections in the curve (Fig. 4) at mole ratios of $V : NH_4$ ($= R$) of 2 : 1 and 1 : 1 (at pH values of about 5·5 and 7·5) in the titration of vanadic acid with ammonia solution.

TABLE 7. *Wavelengths corresponding to a transmission density of* 50% *for vanadate solutions* (0·025 *g.-atom/l.*) *in* 1 *cm. cells.*

pH	8·8	8·5	8·0	7·5	6·7	6·6	6·45	6·4	5·2	3·9
Wavelength (Å)	3860	3880	3870	3870	4680	4990	5090	5180	5210	5180

The rapid conversion of trivanadate into tetravanadate and thence into hexavanadate in region pH 7—5 does in fact coincide with a shift in the edge of an absorption band in the spectra of the vanadates in aqueous solution (0·025 g.-atom/l.). This can be seen from Table 7 where the values of 50% transmittency are shown. This shift results in the appearance of a yellow or orange colour.

It is evident that the tendency for inorganic complex cations to be inhibited in their exchange reactions with tightly cross-linked resins, observed by Gustavson and Holm,[17] is also shown by the reactions of complex anions with the corresponding exchangers (cf. ref. 18), and in the case of the bulky isopolyvanadate ions to permit separation by the ionic-sieve effect.

The authors thank Dr. Arden of the Permutit Company for providing a very wide range of DeAcidite F.F. samples of varying weight-swellings, and Miss McPartlin for determining the weight-swelling values of a number of samples; one of us (R. U. R.) expresses his gratitude to the Permutit Company for a postgraduate scholarship.

CHEMISTRY DEPARTMENT, BATTERSEA COLLEGE OF TECHNOLOGY, LONDON, S.W.11. [*Received, July 24th,* 1958.]

[17] Gustavson and Holm, *Svensk Kem. Tidskr.*, 1952, **64**, 137.
[18] Herber, Tongue, and Irvine, *J. Amer. Chem. Soc.*, 1955, **77**, 5840.

---

950. *The Relation between Dextro- and* iso*Dextro-pimaric Acid.*

By B. GREEN, ADELAIDE HARRIS, and W. B. WHALLEY.

Dextro- and *iso*dextro-pimaric acid have been shown to be epimeric at positions 7 and 13.*

THE structures of dextro- and *iso*dextro-pimaric acid have been well established,[2,3] together with the stereochemistry at positions 1, 11, and 12 which is identical with that of abietic acid [2] as in (I). Neither the relative nor the absolute configurations at positions 7 and 13 in these acids have been defined unequivocally although this is a problem not only of chemical but also of possible biogenetic significance (cf. Wenkert [4]).

Harris and Sanderson [2] converted dihydrodextropimaric acid into the keto-aldehyde (II), by ozonolysis, and thence by reduction and dehydrogenation into the hydrocarbon (III) which was also obtained from dihydro*iso*dextropimaric acid by the same reactions. These results were construed as proof that dextro- and *iso*dextro-pimaric acid are epimeric

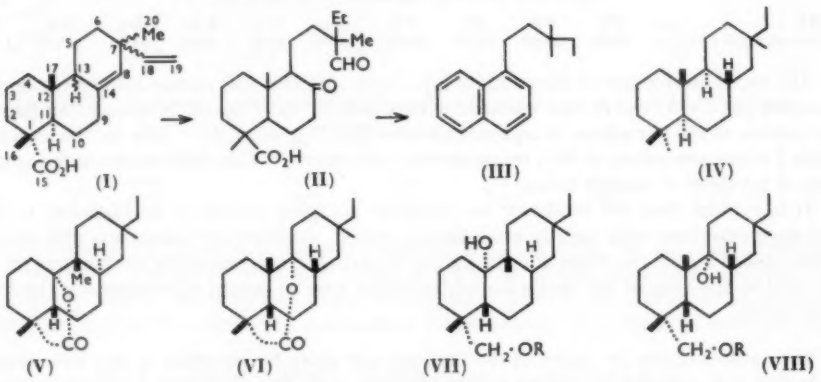
* Some of this work have been the subject of a preliminary communication.[1]

[1] Green, Harris, and Whalley, *Chem. and Ind.*, 1958, 1084.
[2] Harris and Sanderson, *J. Amer. Chem. Soc.*, 1948, **70**, 2081.
[3] Simonsen and Barton, "The Terpenes," Cambridge Univ. Press, London, 1952, Vol. III, p. 447.
[4] Wenkert, *Chem. and Ind.*, 1955, 284.

XUM

at position 7, but are equally compatible with the view that the two precursors of (III) are epimeric at position 13,[4] or as we indicate below, at both these positions.*

Dihydro*iso*dextropimaric acid (infrared absorption at 825 cm.$^{-1}$; >C=CH–) is converted by concentrated sulphuric acid into a mixture of a γ-lactone (infrared absorption at 1773 cm.$^{-1}$) and a δ-lactone (infrared absorption at 1724 cm.$^{-1}$) which are formulated as 12α-hydroxy-13β-methyl-12-nor-11β-7-*allo*pimaran-15-oic lactone (V) and 13-hydroxy-11β-7-*allo*pimaran-15-oic lactone (VI) respectively, by analogy with the corresponding products derived from dihydrodextropimaric acid.[6]



Collateral evidence in support of structures (V) and (VI) and hence for the analogous, similarly derived γ- and δ-lactones of dihydrodextropimaric acid [6] is provided by the reduction of the δ-lactone (VI) with lithium aluminium hydride to 11β-7-*allo*pimarane-13 : 15-diol (VIII; R = H) which, in accordance with this formula, furnishes a monoacetate (VIII; R = Ac) which has infrared absorption (in Nujol) at 3534 (OH) and 1724 cm.$^{-1}$ (acetate). The γ-lactone (V) similarly furnishes the diol (VII; R = H) which in turn yields a monoacetate (VII; R = Ac) with infrared absorption (in Nujol) at 3436 (OH) and 1721 cm.$^{-1}$ (acetate).

The formation of these two lactones which differ from the corresponding γ- and δ-lactones derived from dihydrodextropimaric acid, under similar conditions during which the stereochemistry at all centres except $C_{(1)}$ and $C_{(7)}$ may be disturbed, indicates that dextro- and *iso*dextro-pimaric acid are epimeric at least at position 7,† and that pimara- and 7-*allo*pimara-8(14) : 18-dienes occur naturally [7-*allo*pimara-9(14) : 18-dien-15-oic acid [7,9] belongs to the same $C_{(7)}$-series], and thus the hypothesis [4] that only pimara-8(14) : 18-dienes having quasi-axial vinyl groups occur naturally is untenable.

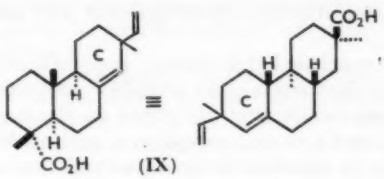
The well-established stability of dextropimaric acid to mineral acids [10] indicates that the 12-methyl group and the 13-hydrogen atom are *trans* to one another as in (IX). This conclusion has been substantiated by molecular-rotational data.[5] In addition, if dextropimaric acid is correctly represented by (IX) ring C of this acid must be analogous to ring A

* For nomenclature Klyne's suggestions [5] have been modified and the name pimarane is now allocated to the hydrocarbon (IV) which has the same configuration at position 7 as dextropimaric acid, whilst the hydrocarbon (IV), having the epimeric configuration at position 7, *i.e.*, as in *iso*dextropimaric acid, is called 7-*allo*pimarane. We are indebted to the Editor for helpful comment on these proposals.

† Preliminary communications by Edwards and Howe,[7] and by Wenkert and Chamberlin [8] published during the preparation of this manuscript confirm our conclusion.

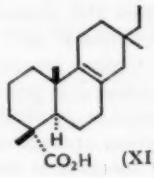
[5] Klyne, *J.*, 1953, 3072.
[6] Le Van Thoi and Ourgaud, *Bull. Soc. chim. France*, 1956, 202.
[7] Edwards and Howe, *Chem. and Ind.*, 1958, 629.
[8] Wenkert and Chamberlin, *J. Amer. Chem. Soc.*, 1958, **80**, 2912.
[9] Ukita, Tsumita, and Utsugi, *Pharm. Bull.* (*Japan*), 1955, **3**, 441.
[10] Ref. 4, p. 448 and references therein.

of cholest-4-ene (X) (cf. Klyne [5] and Djerassi *et al.*[11]) which has a positive Δ(C:C) value, *viz.*, $(+240°) - (+91°) = +149°$. Dihydrodextropimaric acid has a small but positive Δ(C:C) value $= (+60°) - (+55°) = +5°$, confirming the structure (IX).

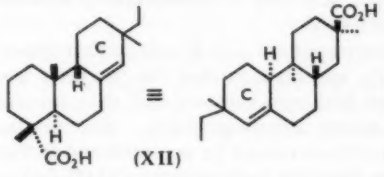


(IX)

(X)

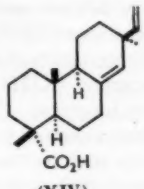


(XI)

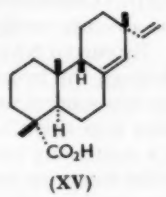


(XII)

(XIII)



(XIV)



(XV)

When treated with dilute hydrochloric acid under conditions of much less severity than those which do not isomerise dextropimaric acid,[12] dihydro*iso*dextropimaric acid readily yields 7-*allo*pimar-13(14)-en-15-oic acid (XI), which is devoid of infrared absorption at 825 cm.$^{-1}$ (absence of $>$C=CH$-$), may be formed more readily by use of toluene-*p*-sulphonic acid in benzene, and is lactonised to the γ-lactone (V). Similarly, *iso*dextropimaric acid furnishes 7-*allo*pimara-13(14) : 18-dien-15-oic acid which is hydrogenated to (XI). The ease of transformation of dihydro*iso*dextropimaric acid to 7-*allo*pimar-13(14)-en-15-oic acid (XI) indicates that dextro- and *iso*dextro-pimaric acid are epimeric at position 13, and thus in *iso*dextropimaric acid the 12-methyl group and the 13-hydrogen atom are *cis* to one another as in (XII). The molecular-rotational evidence supports this thesis.

The contribution of $C_{(7)}$ to the molecular rotation is negligible, as is apparent from, *inter alia*, (*a*) the close similarity of the $[M]_D$ values for dextropimar-13(14)-en-15-oic acid $(+224°)$ and *iso*dextropimar-13(14)-en-15-oic acid $(+234°)$, (*b*) the very similar $[M]_D$ values for tetrahydrodextropimaric acid $(+55°)$ and for tetrahydro*iso*dextropimaric acid $(+73°)$, (*c*) the almost identical $\Delta[M]_D$ values, *viz.*, $(+234°) - (-43°) = 277°$, and $(+221°) - (-52°) = 273°$, for the conversion of dextropimar-13(14)-en-15-oic acid and *iso*dextropimar-13(14)-en-15-oic acid into the respective γ-lactones (V), and (*d*) the $\Delta[M]_D$ values, *viz.*, $(+234°) - (-121°) = +355°$, and $(+221°) - (-137°) = +358°$, for conversion of the same pair of acids into the corresponding δ-lactones (VI).

Thus, when considering the molecular-rotational data for dextro- and *iso*dextropimaric acid it may be regarded as established that the contribution of $C_{(7)}$ is negligible and since the stereochemistry at positions 1, 11, and 12 is identical any significant variation from the expected values may be attributed to stereochemical differences at position 13. Thus $\Delta[M]_D$ for the conversion of dihydro*iso*dextropimaric acid into the γ-lactone (V) $= (-16°) - (-43°) = +27°$, and into the δ-lactone (VI) $\Delta[M]_D = (-16°) - (-122°) = +106°$, whilst the figures for the conversion of dihydrodextropimaric acid into the γ-lactone (V) are $(+60°) - (-52°) = +112°$ and into the δ-lactone (VI) are $(+60°) - (-137°) = +197°$. These results strongly indicate that the configurations at position 13 in dihydrodextro- and in dihydro*iso*dextro-pimaric acid are not identical, *i.e.*, the acids are epimeric. Additional evidence for this view is afforded by the fact that if dihydro*iso*dextropimaric

[11] Djerassi, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6362.
[12] Vesterberg, *Ber.*, 1886, **19**, 2167.

XUM

acid is correctly represented by (XII) then the surroundings of the double bond in ring C are enantiomeric to those in ring A of cholest-4-ene (X) (cf. Klyne [5]) which has $\Delta(C{:}C) = +149°$. Using tetrahydro*iso*dextropimaric acid [7] as the saturated reference compound we have $\Delta(C{:}C)$ in dihydro*iso*dextropimaric acid $= (-16°) - (+73°) = -89°$, a result which substantiates the stereochemistry (XII) for dihydro*iso*dextropimaric acid and hence for *iso*dextropimaric acid.

From surface-tension measurements Bruun [13] concluded that dextro- and *iso*dextropimaric acid are epimeric at position 7 and that the vinyl residues are probably quasi-axial and quasi-equatorial respectively. Although these results were calculated on the basis of the *trans-anti-trans* arrangement of rings A, B, and C in *iso*dextropimaric acid models indicate that his conclusions would probably not be invalidated by its formulation as (XII). Consequently dextro- and *iso*dextro-pimaric acid may be provisionally allocated the absolute configurations (XIV) and (XV) respectively.

By partial dehydrogenation of dextro- and *iso*dextro-pimaric acid Harris and Sanderson [2] obtained the hydrocarbon (XIII) in small quantity and claimed that the products from the two sources were identical. The hydrocarbons had zero rotation and thus racemisation at position 7 was assumed to have occurred during dehydrogenation. Racemisation of a quaternary centre such as this under these conditions cannot be accepted and in view of the foregoing considerations it is most probable that the hydrocarbons (XIII) derived from dextro- and *iso*dextro-pimaric acid are *not* identical but are enantiomeric and have very small molecular rotations.

Experimental

*Lactonisation of Dihydro*iso*dextropimaric Acid.*—A solution of dihydro*iso*dextropimaric acid (0·5 g.), $[\alpha]_D^{18}$ −5°, in concentrated sulphuric acid (5 ml.) was kept at room temperature for 15 min., then poured on ice. After isolation with ether, the extract was washed with 2N-sodium hydroxide and with water, dried, and evaporated to an oil (0·4 g.), $\nu_{max.}$ 1724 and 1773 cm.$^{-1}$. Purification from methanol gave 12α-*hydroxy*-13β-*methyl*-12-*nor*-11β-7-allo-*pimaran*-15-*oic lactone* in prisms (200 mg.), m. p. 108°, $[\alpha]_D$ −14° (Found: C, 78·9; H, 10·6. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%). Harris and Sanderson [2] record m. p. 109—110° for an uncharacterised lactone which is probably identical with our preparation, derived from dihydro-*iso*dextropimaric acid.

Reduction of this lactone (0·04 g.) in boiling ether (25 ml.) containing lithium aluminium hydride (0·1 g.) during 10 hr. furnished 13β-methyl-12-nor-11β-7-*allo*pimarane-12α : 15-diol which formed prisms (0·02 g.), m. p. 184°, from ethyl acetate. Prepared by the action of acetic anhydride–pyridine at room temperature during 10 hr., 15-*acetoxy*-13β-*methyl*-12-*nor*-11β-7-allo*pimaran*-12α-*ol* separated from aqueous methanol in prisms, m. p. 84° (Found: C, 74·8; H, 10·7. $C_{22}H_{38}O_3$ requires C, 75·4; H, 10·9%).

The mother-liquors from the purification of the γ-lactone (V) contained a δ-lactone which was more readily obtained when a solution of dihydro*iso*dextropimaric acid (500 mg.) in concentrated sulphuric acid (10 ml.) was kept at room temperature during 24 hr. Isolated in the usual manner and purified from aqueous methanol or light petroleum (b. p. 40—60°) at 0°, 13-*hydroxy*-11β-7-allo*pimaran*-15-*oic lactone* formed prisms (300 mg.), m. p. 62°, $[\alpha_D^{18}]$ −37°, readily soluble in organic solvents (Found: C, 78·5; H, 10·6. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%).

Reduction of this lactone (0·14 g.) in boiling ether (25 ml.) containing lithium aluminium hydride (0·2 g.) during 16 hr. furnished 11β-7-allo*pimarane*-13 : 15-*diol* which separated from ethyl acetate in needles (0·08 g.), m. p. 142° (Found: C, 77·7; H, 11·7. $C_{20}H_{36}O_2$ requires C, 77·9; H, 11·8%). Formed by the action of acetic anhydride–pyridine at room temperature during 24 hr., 11β-15-*acetoxy*-7-allo*pimaran*-13-*ol* separated from aqueous methanol in prisms, m. p. 83° (Found: C, 74·6; H, 10·7. $C_{22}H_{38}O_3$ requires C, 75·4; H, 10·9%).

7-allo*Pimar*-13(14)-*en*-15-*oic Acid.*—(*a*) A solution of *iso*dextropimaric acid (0·5 g.) in benzene (20 ml.) containing toluene-*p*-sulphonic acid (25 mg.) was refluxed for 1 hr., cooled, washed with water, dried, and evaporated, to furnish 7-allo*pimar*-13(14) : 18-*dien*-15-*oic acid* which separated from aqueous methanol in needles, or from aqueous acetic acid in prisms (0·5 g.), m. p. 118°, $[\alpha]_D^{19}$ +58° (Found: C, 79·0; H, 10·6. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%).

[13] Bruun, *Acta Acad. Aboensis, Math. Phys.*, 1954, **19**, (3), 7.

Hydrogenation of 7-*allo*pimara-13(14) : 18-dien-15-oic acid (0·4 g.) in methanol (50 ml.) containing platinic oxide (0·05 g.) was complete in 20 min., and 7-allo*pimar*-13(14)-*en*-15-*oic acid* separated from aqueous methanol in prisms (0·4 g.), m. p. 110°, $[\alpha]_D^{20}$ +60° (Found: C, 79·2; H, 11·0. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%). Lactonisation of this acid (200 mg.) with sulphuric acid as previously described gave the γ-lactone (100 mg.), m. p. and mixed m. p. 108°, having the requisite infrared spectrum. A mixed m. p. with dihydro*iso*dextropimaric acid was *ca.* 102°.

(*b*) Isomerisation of dihydro*iso*dextropimaric acid (0·5 g.) with toluene-*p*-sulphonic acid (50 mg.) in boiling benzene (50 ml.) during 1 hr. furnished 7-*allo*pimar-13(14)-en-15-oic acid in prisms (0·5 g.) [m. p. and mixed m. p. with the preparation (*a*); infrared spectrum].

(*c*) Dihydro*iso*dextropimaric acid (0·2 g.) in alcohol (50 ml.) containing 10N-hydrochloric acid (1 ml.) was refluxed for 3 hr., then diluted with water, and the sticky precipitate was repeatedly crystallised from aqueous methanol, to furnish 7-*allo*pimar-13(14)-en-15-oic acid (50 mg.), identical with the compound prepared by methods (*a*) and (*b*).

The authors are grateful to Dr. R. V. Lawrence, U.S. Department of Agriculture, Olustee, Florida, for a gift of *iso*dextropimaric acid, to Dr. Le Van Thoi (formerly of Paris, now of the University of Saigon) for specimens of the γ- and the δ-lactone derived from dihydrodextropimaric acid, and to Professor E. Wenkert for informing us of his results in this field before their publication.

Rotations refer to ethanol solutions and the infrared absorption spectra to CCl_4 solutions (Perkin-Elmer Model 21 spectrophotometer).

UNIVERSITY OF LIVERPOOL. [*Received, August 12th,* 1958.]

---

951. 1 : 7 : 10- *and* 1 : 6 : 10-*Trimethylphenanthrene.*

By J. A. CORRAN and W. B. WHALLEY.

The compounds named in the title have been synthesised by standard methods.

DURING degradative studies concerning the constitution of the fungal diterpene rosololactone,[1] 1 : 7 : 10- and 1 : 6 : 10-trimethylphenanthrene have been synthesised as reference compounds, by standard methods.

Condensation of 1 : 8-dimethylnaphthalene with methylsuccinic anhydride by the Friedel–Crafts method furnished a mixture of acids (I; R = H, R′ = Me, and *vice versa*). Reduction of the keto-acid (I; R = H, R′ = Me) by the Huang-Minlon [2] modification of the Wolff–Kishner method gave γ-(4 : 5-dimethyl-1-naphthyl)-α-methylbutyric acid (II; R = H, R′ = Me), the acid chloride of which was cyclised to 1 : 2 : 3 : 4-tetrahydro-2 : 8 : 9-trimethyl-1-oxophenanthrene (III; R = H, R′ = Me). Reduction of this cyclic ketone by a second application of the Huang-Minlon process yielded 1 : 2 : 3 : 4-tetrahydro-2 : 8 : 9-trimethylphenanthrene (IV; R = H, R′ = Me) which furnished 1 : 7 : 10-trimethylphenanthrene on dehydrogenation.

Similarly 1 : 6 : 10-trimethylphenanthrene was prepared from the acid (I; R = Me, R′ = H) by the stages (II), (III), and (IV; R = Me, R′ = H).

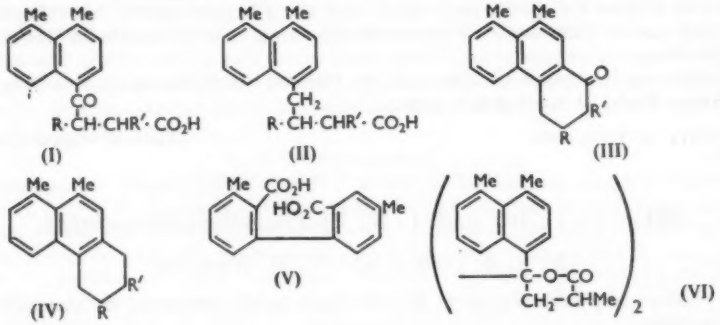
Reduction of β-(4 : 5-dimethyl-1-naphthoyl)-α-methylpropionic acid (I; R = H, R′ = Me) by the Clemmensen method furnished a product which, in agreement with the analytical data and infrared absorption at 1783 $cm.^{-1}$, is formulated as the pinacol-di-γ-lactone (VI) (cf. Huang-Minlon [2]).

In accordance with general principles the condensation of 1 : 8-dimethylnaphthalene with methylsuccinic anhydride could furnish either the 2- or the 4-naphthoylpropionic acid. Since the ultraviolet absorption spectra show conclusively that the final tricyclic hydrocarbons are phenanthrenes and not anthracenes, it follows that the condensation

[1] Harris, Robertson, and Whalley, *J.*, 1958, 1807; and unpublished work from these laboratories.
[2] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.

XUM

furnishes the 4-naphthoylpropionic acids (I), as expected. Exclusive production of 4-substituted naphthalenes has been observed in analogous Friedel–Crafts condensations between succinic anhydride and 1-methylnaphthalene [3] and acenaphthene.[4] The orientation of the two trimethylphenanthrenes and hence of the cognate derivatives follows from the structures of the isomeric cyclic ketones (III; R = H, R′ = Me and *vice versa*). The comparatively slow rate of reduction of one ketone (IIIA) in the Wolff–Kishner reaction together with its reluctance to form a 2 : 4-dinitrophenylhydrazone, in contrast to the isomer (B) which furnishes a derivative immediately and is more rapidly reduced by the Wolff–Kishner method, indicate steric hindrance in the isomer (A) which may thus be formulated as 1 : 2 : 3 : 4-tetrahydro-2 : 8 : 9-trimethyl-1-oxophenanthrene (III; R = H, R′ = Me). Rates of formation of ketonic derivatives have been used [5] to distinguish between 2(or 8)-methyl- and 2 : 8-dimethyl-1-tetralones. Collateral evidence for the assignments is that the cyclic ketone formulated as (III; R = H, R′ = Me) does not furnish a piperonylidene derivative, whilst the isomer (III; R = Me, R′ = H) does.



Attempts to oxidise the two trimethylphenanthrenes to dimethyl-2 : 2′-diphenic acids with hydrogen peroxide–acetic acid gave intractable products, although 1 : 7-dimethylphenanthrene readily furnished 3 : 4′-dimethyl-2 : 2′-diphenic acid (V), the expected oxidation product from 1 : 7 : 10-trimethylphenanthrene.

Improvements in the synthesis of 9-methoxy-1 : 7-dimethylphenanthrene are recorded below.

Experimental

1 : 8-*Dimethylnaphthalene*.—Finely divided naphthalic anhydride (10 g.) was reduced when extracted from a Soxhlet thimble by a refluxing suspension of lithium aluminium hydride (5 g.) in ether (500 ml.) during 100 hr. Excess of reagent was destroyed by ethyl acetate, and the reaction complex decomposed with 2N-sulphuric acid (400 ml.). Evaporation of the washed ethereal extract furnished 1 : 8-di(hydroxymethyl)naphthalene which separated from benzene in needles (6 g.), m. p. 158°. Ghilardi and Kalopissis [6] record m. p. 154—155°.

Concentration of the benzene mother-liquors furnished a product which on chromatography from benzene on aluminium oxide gave 8-*hydroxymethyl*-1-*naphthoic lactone* (*ca.* 0·5 g.) which separated from benzene–light petroleum (b. p. 80—100°) in plates, m. p. 157° (Found: C, 78·4; H, 4·5. $C_{12}H_8O_2$ requires C, 78·3; H, 4·4%), $\nu_{max.}$ 1727 cm.$^{-1}$ (lactone). The mixed m. p. with naphthoic anhydride or 1 : 8-di(hydroxymethyl)naphthalene was depressed. This lactone was insoluble in cold 2N-aqueous sodium hydroxide but dissolved in hot aqueous-alcoholic 2N-sodium hydroxide to furnish a solution which remained clear on dilution and from which the parent lactone was precipitated by acid. Reduction of this lactone with lithium aluminium

[3] Haworth and Mavin, *J.*, 1932, 2720.
[4] Fieser and Peters, *J. Amer. Chem. Soc.*, 1932, **54**, 4347.
[5] Cocker, Fateen, and Lipman, *J.*, 1951, 926.
[6] Ghilardi and Kalopissis, *Bull. Soc. chim. France*, 1952, 217.

hydride gave 1 : 8-di(hydroxymethyl)naphthalene, m. p. 62°, by the method of Ghilardi and Kalopissis,[6] who record no yield.

1 : 7 : 10-*Trimethylphenanthrene.*—Aluminium chloride (8·3 g.), dissolved in nitrobenzene (15 ml.), was added slowly to a stirred solution of 1 : 8-dimethylnaphthalene (5 g.) and methylsuccinic anhydride (3·7 g.) in nitrobenzene (15 ml.) at 0°, and 5 days later the mixture was decomposed by ice and excess of hydrochloric acid and extracted with ether. Distillation of the ether, followed by removal of the nitrobenzene in a current of steam, furnished a resinous, acid which was esterified by boiling 10% alcoholic sulphuric acid for 4 hr. Isolated in the usual manner followed by distillation, the mixed esters (5·3 g.) had b. p. 185—195°/0·2 mm., and were saponified by refluxing them for 1 hr. with potassium hydroxide (1 g.) in water (50 ml.) and alcohol (50 ml.). Isolation with ether from the cooled, acidified hydrolysate, followed by purification from benzene–light petroleum (b. p. 80—100°), gave *γ-(4 : 5-dimethyl-1-naphthyl)-α-methyl-γ-oxobutyric acid* (2·7 g.) as plates, m. p. 139—141°, unchanged by further crystallisation or by chromatography on silica–Celite (Found: C, 75·3; H, 6·8. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%). The mother-liquor from this acid slowly deposited a semi-crystalline acid (1·5 g.) which on repeated purification from benzene–light petroleum (b. p. 60—80°) gave *γ-(4 : 5-dimethyl-1-naphthyl)-β-methyl-γ-oxobutyric acid* in pale yellow needles, m. p. 137—138° (Found: C, 75·6; H, 6·8%). Occasionally the acids separated in the reverse order during purification from benzene–light petroleum (b. p. 60—80°).

Fractional distillation of the methylated mixture did not achieve a more satisfactory separation of these two acids since hydrolysis of each fraction furnished a crystalline acid, m. p. 139—141°, together with the semi-crystalline butyric acid. The mixed m. p. of these acids was undepressed.

A mixture of the above α-methylpropionic acid (2 g.), 100% hydrazine hydrate (0·6 ml.), potassium hydroxide (1·3 g.), and diethylene glycol (25 ml.) was refluxed at 170—180° for 2 hr., then excess of hydrazine and water were removed by distillation until the reaction temperature, which was maintained for a further 3 hr., was 220°. Isolated with ether from the cooled, acidified reaction mixture, the product was purified by chromatography (silica) from chloroform–light petroleum (b. p. 60—80°) (1 : 10), to give *γ-(4 : 5-dimethylnaphthyl)-α-methylbutyric acid* which separated from light petroleum (b. p. 80—100°) in prisms (1·2 g.), m. p. 92° (Found: C, 79·5; H, 7·8. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·9%).

The acid (I; R = H; R′ = Me) (0·5 g.) was esterified with diazomethane, and the oily ester reduced by refluxing it for 36 hr. with 25% hydrochloric acid (7 ml.), toluene (3 ml.), zinc amalgam (1 g.), and acetic acid (0·5 ml.): additional quantities (1·5 ml.) of concentrated hydrochloric acid were added at six-hourly intervals. Isolated with ether, the *di-γ-lactone* (VI) of 4 : 5-bis-(4 : 5-dimethyl-1-naphthyl)-4 : 5-dihydroxy-2 : 7-dimethyloctane-1 : 8-dioic acid separated from benzene–light petroleum (b. p. 60—80°) in needles (0·05 g.), m. p. 282° [Found: C, 80·3; H, 7·0%; *M* (Rast), 467. $C_{34}H_{34}O_4$ requires C, 80·6; H, 6·8%; *M*, 507]. This substance was insoluble in 2N-sodium hydrogen carbonate but readily dissolved in warm aqueous-alcoholic sodium hydroxide to furnish a solution which remained clear on dilution and from which acid precipitated the parent lactone.

A solution of *γ-(4 : 5-dimethyl-1-naphthyl)-α-methylbutyryl chloride* [prepared from the acid (1 g.) and phosphorus pentachloride (0·9 g.)] in tetrachloroethane (10 ml.) was added slowly to a stirred suspension of aluminium chloride (0·7 g.) in tetrachloroethane (10 ml.) at 0°. 24 Hr. later the mixture was decomposed by ice and excess of 2N-hydrochloric acid, the tetrachloroethane removed by distillation with steam, the residue extracted with ether, and the extract washed with 2N-hydrochloric acid, water, 2N-sodium hydrogen carbonate, dried, and evaporated to yield a semi-crystalline solid which was purified by chromatography from light petroleum (b. p. 60—80°) on aluminium oxide. Purification of the eluate from light petroleum (b. p. 40—60°) furnished 1 : 2 : 3 : 4-*tetrahydro*-2 : 8 : 9-*trimethyl*-1-*oxophenanthrene* in prisms (0·6 g.), m. p. 84°, $\lambda_{max.}$ 216, 256, 281, 291, 351, (log ε 5·34, 5·74, 4·83, 4·90, 4·29 respectively) (Found: C, 85·4; H, 7·9. $C_{17}H_{18}O$ requires C, 85·7; H, 7·6%).

This ketone in alcohol did not give a derivative with alcoholic 2 : 4-dinitrophenylhydrazine sulphate during 24 hr. at room temperature. However the derivative separated when the mixture was heated on the steam-bath for 20 min. Purification from benzene–ethanol gave the 2 : 4-*dinitrophenylhydrazone* in scarlet needles, m. p. 242 (Found: C, 66·3; H, 5·3; N, 13·2. $C_{23}H_{22}O_4N_4$ requires C, 66·0; H, 5·3; N, 13·4%). When a solution of the ketone (0·05 g.) and piperonaldehyde (0·03 g.) in alcohol (1 ml.) containing 1% alcoholic sodium ethoxide (1 ml.)

XUM

was heated on the steam-bath during 3 hr., no piperonylidene derivative was obtained but unchanged ketone (0·04 g.), m. p. and mixed m. p. 82—83°, was recovered.

Reduction of the foregoing ketone (0·7 g.) with hydrazine hydrate (0·25 ml.), potassium hydroxide (0·4 g.), and diethylene glycol (12 ml.) was carried out at 140° for 2 hr. and then at 200° for 4 hr. after removal of excess of hydrazine. Isolated with ether the product was separated by chromatography from light petroleum (b. p. 60—80°) on activated aluminium oxide into unchanged starting material (0·3 g.) and 1 : 2 : 3 : 4-*tetrahydro*-2 : 8 : 9-*trimethylphenanthrene* (0·3 g.), b. p. 170—180°/0·1 mm., m. p. 38—40° (Found: C, 90·6; H, 9·0. $C_{17}H_{20}$ requires C, 91·0; H, 9·0%).

A mixture of this tetrahydrophenanthrene (1·2 g.), and 30% palladium–charcoal (0·1 g.) was heated under reflux at 300° for 2 hr. and then at 350° for ½ hr. The cooled mixture was extracted with benzene, and the crude product purified by chromatography from the same solvent on activated aluminium oxide, to give 1 : 7 : 10-*trimethylphenanthrene* which separated from light petroleum (b. p. 40—60°) in plates (1 g.), m. p. 93°, $\lambda_{max.}$ 224, 258, 280, 290, 302, 318, 327, 334, 351 (log ε 4·28, 4·74, 4·07, 3·97, 4·05, 2·56, 2·40, 2·52, and 2·23 respectively) (Found: C, 92·0; H, 7·6. $C_{17}H_{17}$ requires C, 92·7; H, 7·3%). The *picrate* separated from alcohol in orange needles, m. p. 149° (Found: C, 61·7; H, 4·1; N, 9·3. $C_{23}H_{19}O_7N_3$ requires C, 61·5; H, 4·3; N, 9·4%).

1 : 6 : 10-*Trimethylphenanthrene.*—The Wolff–Kishner reduction of γ-(4 : 5-dimethyl-1-naphthyl)-β-methyl-γ-oxobutyric acid (1·3 g.) by the method used for the isomer furnished γ-(4 : 5-dimethyl-1-naphthyl)-β-methylbutyric acid which separated from light petroleum (b. p. 80—100°) in prisms (0·4 g.), m. p. 87°. The mixed m. p. with the isomeric acid was undepressed.

Cyclisation of the acid chloride (0·4 g.) of this acid in tetrachloroethane (5 ml.) containing aluminium chloride (0·3 g.) at 0° furnished 1 : 2 : 3 : 4-*tetrahydro*-3 : 8 : 9-*trimethyl*-1-*oxophenanthrene* which separated from light petroleum (b. p. 40—60°) in needles (0·2 g.), m. p. 94°, $\lambda_{max.}$ 218, 260, 286, 295, 306, 360 (log ε 5·30, 5·68, 4·85, 4·92, 4·77, and 4·51 respectively) (Found: C, 85·9; H, 7·5%). The mixed m. p. with the isomeric 1 : 2 : 3 : 4-tetrahydro-2 : 8 : 9-trimethyl-oxophenanthrene was depressed. When a solution of alcoholic 2 : 4-dinitrophenylhydrazine sulphate was added to a cold solution in alcohol of this ketone the 2 : 4-*dinitrophenylhydrazone* separated rapidly and was purified from benzene–ethyl acetate, forming red needles, m. p. 305° (decomp.) (Found: C, 65·7; H, 5·1; N, 13·2%). Prepared from this ketone (0·1 g.) and piperonaldehyde (0·1 g.) in alcohol (3 ml.) containing 1% alcoholic sodium ethoxide (1 ml.) on the steam-bath during 3 hr., the difficultly purifiable piperonylidene derivative separated from benzene–acetone in pale yellow needles, m. p. 226°; insufficient material was obtained for analysis. No unchanged ketone was recovered.

Reduction of this ketone (1·9 g.) with 100% hydrazine hydrate (0·75 ml.), potassium hydroxide (1·35 g.), and diethylene glycol (25 ml.) proceeded completely during 2 hr. at 140° followed by 4 hr. at 200°, to furnish 1 : 2 : 3 : 4-*tetrahydro*-3 : 8 : 9-*trimethylphenanthrene* in needles (1·6 g.), m. p. 63° [from light petroleum (b. p. 40—60°)] (Found: C, 90·8; H, 8·9%).

Dehydrogenation of this tetrahydrophenanthrene (1·1 g.) with 30% palladium–charcoal (0·1 g.) as before furnished 1 : 6 : 10-*trimethylphenanthrene*, needles (1 g.) [from methanol or light petroleum (b. p. 40—60°)], m. p. 83°, $\lambda_{max.}$ 216, 260, 283, 292, 305, 325, 340, 357 (log ε, 4·52, 4·82, 4·15, 4·04. 4·07, 2·68, 2·87, and 2·70 respectively) (Found: C, 92·4; H, 7·1%). The mixed m. p. with the isomeric phenanthrene was depressed. The *picrate* separated from alcohol in orange needles, m. p. 140° (Found: C, 61·6; H, 4·1; N, 9·0%) (the mixed m. p. with the isomeric picrate was depressed).

3 : 4′-*Dimethyl*-2 : 2′-*diphenic Acid.*—Hydrogen peroxide (1·7 ml. of 30%) was added gradually to a solution of 1 : 7-dimethylphenanthrene (0·5 g.) in acetic acid (6 ml.) at 80°. After 3 hr. at this temperature the acetic acid was removed by distillation, and a solution in benzene of the residual oil was washed with 2N-sodium hydrogen carbonate. Acidification of the alkaline extract furnished a solid which, after purification by chromatography from chloroform on silica, gave 3 : 4′-*dimethyl*-2 : 2′-*diphenic acid* which separated from benzene–light petroleum (b. p. 60—80°) in needles (0·2 g.), m. p. 205° (decomp.) (Found: C, 71·1; H, 5·3. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%).

1 : 7-*Dimethyl*-9-*methoxyphenanthrene.*—The following improvements were effected in the synthesis recorded by Ruzicka and Waldmann.[7]

Dehydrogenation of 7-methyl-1-tetralone [7] (10·1 g.) with 30% palladium–charcoal (0·5 g.)

[7] Ruzicka and Waldmann, *Helv. Chim. Acta*, 1932, **15**, 907.

was effected at 320° for 3 hr., then the cooled reaction mixture was extracted with ether and the extract washed with 2N-sodium hydroxide. Acidification of this furnished 7-methyl-1-naphthol which separated from light petroleum (b. p. 80—100°) in needles (6·1 g.), m. p. 111°. Ruzicka and Waldmann [7] record m. p. 110—111°. The neutral fraction from the dehydrogenation gave 2-methylnaphthalene (3 g.), m. p. and mixed m. p. 34°.

Reduction of γ-(4-methoxy-6-methyl-1-naphthyl)-γ-oxobutyric acid [7] (5 g.) with 100% hydrazine hydrate (1·4 g.), potassium hydroxide (3·1 g.), and diethylene glycol (60 ml.) was achieved under reflux for 1 hr. at 180—190° and then for 4 hr. at 205—225°. The cooled mixture was diluted with water and extracted with ether. The ethereal extract was washed with 2N-sodium hydrogen carbonate, and the washings were acidified. Methylation of the dried precipitate with methyl sulphate–potassium carbonate in boiling acetone during 6 hr. furnished methyl γ-(4-methoxy-6-methyl-1-naphthyl)butyrate which was purified by chromatography from benzene, followed by elution with benzene–light petroleum (b. p. 60—80°) on neutralised aluminium oxide. Saponification of this ester gave γ-(4-methoxy-6-methyl-1-naphthyl)butyric acid (2·6 g.) in needles, m. p. 144° (from methanol). Ruzicka and Waldmann [7] record m. p. 142°.

Cyclisation of this acid followed by interaction of the resultant ketone with methylmagnesium iodide according to the method of Ruzicka and Waldmann [7] furnished 1 : 2 : 3 : 4-*tetrahydro*-1-*hydroxy*-9-*methoxy*-1 : 7-*dimethylphenanthrene* which separated from light petroleum (b. p. 60—80°) in needles, m. p. 111°, with infrared absorption at 3393 cm.$^{-1}$ (Found: C, 79·1; H, 7·7. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·9%).

9-Methoxy-1 : 7-dimethylphenanthrene, purified by chromatography from light petroleum (b. p. 40—60°) on activated aluminium oxide, separated from the same solvent in plates, m. p. 131° (Found: C, 85·9; H, 7·0; OMe, 12·8. Calc. for $C_{16}H_{12}$·OMe: C, 86·4; H, 6·8; OMe, 13·1%). Ruzicka and Waldmann [7] record m. p. 126—127°.

The analyses were by Mr. A. S. Inglis, M.Sc., and his associates of this Department. The ultraviolet spectra were determined in alcohol with a Unicam S.P. 500 spectrophotometer, and the infrared spectral data were obtained in Nujol by means of a Grubb-Parsons S3 spectrophotometer. One of us (J. A. C.) is indebted to D.S.I.R. for a Maintenance Grant.

UNIVERSITY OF LIVERPOOL. [*Received, August 12th*, 1958.]

---

952. *Synthesis of Plant-growth Regulators. Part V.** (3-*Substituted* 2-*naphthyloxy*)-n-*alkanecarboxylic Acids.*

By D. WOODCOCK and B. L. DAVIES.

Various (3-substituted 2-naphthyloxy)-*n*-alkanecarboxylic acids have been prepared for testing as parthenocarpic and fungistatic agents. 3-Fluoro-2-naphthol has been prepared and characterised and 3-methyl-2-naphthol has been prepared by an improved method.

MANY substituted 2-naphthyloxyacetic acids are plant-growth regulators and the effect of various nuclear substituents on the activity of the original acid has recently been reported.[1] The complete inactivity of 3-hydroxy-2-naphthyloxyacetic acid,[2] contrasting sharply with the high activity of the corresponding 3-chloro-compound [3] in the tomato ovary test, made it desirable to synthesise and investigate other 3-substituted acids.

3-Methyl-2-naphthol was first prepared by Wolff–Kishner reduction of 3-hydroxy-2-naphthaldehyde, though no analytical details were given.[4] Difficulties in the preparation of the aldehyde led us to prepare 3-methoxy-2-naphthaldehyde by a modified McFadyen–Stevens reaction, Wolff–Kishner reduction of the semicarbazone giving, in addition to

* Part IV, *J.*, 1955, 577.

[1] Luckwill and Woodcock, "Chemistry and Mode of Action of Plant Growth Substances," Butterworths, London, 1956, p. 195.
[2] *Idem*, unpublished work.
[3] *Idem*, *J. Hort. Sci.*, 1955, **30**, 109.
[4] Tishler, Fieser, and Wendler, *J. Amer. Chem. Soc.*, 1940, **62**, 2866.

XUM

3-methyl-2-methoxynaphthalene, a phenolic alcohol which was shown to be 3-hydroxymethyl-2-naphthol Of the 3-halogeno-2-naphthols, the 3-fluoro-compound has not been previously described. Diazotisation of 3-methoxy-2-naphthylamine followed by addition of an aqueous solution of sodium fluoroborate gave 2-methoxy-3-naphthalenediazonium fluoroborate as stable, though photosensitive, orange crystals. This was decomposed by heat to 3-fluoro-2-methoxynaphthalene, and demethylation by hydrobromic acid then gave 3-fluoro-2-naphthol. 3-Bromo-2-naphthol was conveniently prepared from 1 : 3-dibromo-2-naphthol, preferential reduction taking place with hydriodic acid contrary to Clemo and Spence's findings.[5] 3-Cyano-2-naphthol was obtained from the corresponding methyl ether by demethylation with pyridine hydrochloride, since refluxing hydrobromic acid caused hydrolysis in addition to demethylation, forming 3-hydroxynaphthalene-2-carboxyamide. In attempts to obtain 3-iodo-2-naphthol [6] in improved yield, demethylation of 3-iodo-2-methoxynaphthalene gave only β-naphthol, whilst treatment of 3-bromo-2-naphthol with *n*-propyl-lithium, followed by iodine, gave 3-bromo-1-iodo-2-naphthol as a result of hydrogen–lithium exchange in preference to halogen–lithium exchange.[7]

3-Substituted 2-naphthyloxyacetic acids.

			Found (%)				Required (%)		
Substituent	M. p.	Solvent	C	H	N	Formula	C	H	N
F	169—170°	Aq. MeOH	66·0	4·5	—	$C_{12}H_9O_3F$	65·45	4·1	—
Br	175—176	C_6H_6–$COMe_2$	51·1	3·0	—	$C_{12}H_9O_3Br$	51·3	3·2	—
I	173—174	,,	44·0	2·8	—	$C_{12}H_9O_3I$	43·9	2·7	—
Me	188—189	AcOH	71·8	5·6	—	$C_{12}H_{12}O_3$	72·2	5·6	—
OH [a]	166	H_2O	66·3	4·6	—	$C_{12}H_{10}O_4$	66·1	4·6	—
OMe	175—176	Aq. MeOH	66·9	5·3	—	$C_{12}H_{12}O_4$	67·2	5·2	—
NO_2	188—189	,,	57·9	3·6	5·5	$C_{12}H_9O_5N$	58·3	3·6	5·7
CN	147	MeOH	68·9	4·4	6·0	$C_{13}H_9O_3N$	68·7	4·0	6·2
$CO{\cdot}NH_2$	251	,,	63·0	4·7	5·2	$C_{13}H_{11}O_4N$	63·0	4·5	5·7
CO_2H [b]	220—221	AcOH	63·6	4·1	—	$C_{13}H_{10}O_5$	63·4	4·1	—

[a] Shibata and Okuyama (*Bull. Chem. Soc. Japan*, 1936, **11**, 117) give 153°. [b] For details of this preparation see below.

Attempts to prepare 3-amino-2-naphthyloxyacetic acid from the corresponding naphthol by condensation with ethyl bromoacetate gave 3 : 4-dihydro-2-oxonaphtho-[2,3-*b*]-1 : 4-oxazine, but alkaline hydrolysis of this compound gave a solution of the sodium salt suitable for use in the tomato ovary test. The corresponding 2-oxonaphtho-[2,3-*b*]-1 : 4-dioxan was obtained in one attempted methylation of 3-hydroxy-2-naphthyloxyacetic acid.

It is hoped to publish the biological results elsewhere later.

Experimental

3-Methoxy-2-naphthylamine.—In the method of Jambuserwala *et al.*[8] it was found more convenient to use *iso*pentyl rather than the more volatile ethyl nitrite, in the preparation of ethyl 3-methoxy-2-naphthylcarbamate. The latter was hydrolysed by 40% aqueous sodium hydroxide to the amine in 85—98% yield.

3-Methoxy-2-naphthalenediazonium Fluoroborate.—3-Methoxy-2-naphthylamine (10 g.) was dissolved with stirring in a warm mixture of concentrated hydrochloric acid (15 ml.) and water (25 ml.), cooled to 0°, and diazotised by sodium nitrite (4·1 g.) in a little water. After 2 hours' stirring at 7° an ice-cold solution of sodium fluoroborate (8·2 g.) in water (10 ml.) was added and stirring continued for a further 0·5 hr. After the addition of 5% aqueous sodium fluoroborate

[5] Clemo and Spence, *J.*, 1928, 2811.
[6] Goldstein and Cornamusaz, *Helv. Chim. Acta*, 1932, **15**, 935; Goldstein and Gardiol, *ibid.*, 1937, **20**, 516.
[7] Cf. Jones and Gilman, "Organic Reactions," Vol. VI, p. 349.
[8] Jambuserwala, Holt, and Mason, *J.*, 1931, 373.

(40 ml.), the *product* was collected and washed with a little ethyl alcohol followed by dry ether. It crystallised from acetone in orange needles (10·6 g., 68%), m. p. 153° (decomp.), which slowly decompose on exposure to light (Found: N, 10·3. $C_{11}H_9ON_2F_4B$ requires N, 10·3%).

3-Fluoro-2-methoxynaphthalene.—The above diazonium salt (5 g.) was decomposed *in vacuo* at 150—160° (bath-temp.). The *product* (1·3 g., 41%) which distilled was purified by sublimation at 80°/1 mm., followed by crystallisation from light petroleum (b. p. 40—60°). It formed nacreous plates, m. p. 90—91° (Found: C, 75·1; H, 5·2. $C_{11}H_9OF$ requires C, 75·0; H, 5·1%).

3-Fluoro-2-naphthol.—A solution of the above methyl ether (1 g.) in acetic acid (6 ml.) was refluxed for 4 hr. with hydrobromic acid (*d* 1·5; 4 ml.), cooled, diluted with water, and extracted with ether. Naphtholic material, extracted in dilute sodium hydroxide solution, was recovered by acidification and isolation with ether, the ethereal solution dried (Na_2SO_4), and the solvent removed. The residue (0·8 g.), m. p. 70—75°, was purified by sublimation at 80°/1 mm. and crystallised from light petroleum (b. p. 40—60°) in nacreous plates, m. p. 90—91° (Found: C, 74·9; H, 4·1. $C_{10}H_7OF$ requires C, 74·1; H, 4·3%). *3-Fluoro-2-naphthol* depressed the m. p. of its methyl ether to 62°.

N-(3-*Methoxy*-2-*naphthoyl*)-N′-*toluene*-p-*sulphonylhydrazine.*—3-Methoxy-2-naphthhydrazide [8] (18·8 g.) was dissolved in pyridine (50 ml.), cooled, and treated with toluene-*p*-sulphonyl chloride (20 g.) in pyridine (20 ml.). After being heated at 100° for 30 min. the mixture was diluted with water (200 ml.) and acidified with hydrochloric acid, and the crude oily product collected. Washing with dilute hydrochloric acid followed by dissolution in dilute sodium hydroxide and re-precipitation with acid gave a more tractable *product* (22·5 g., 58%) which crystallised from dioxan in monoclinic prisms, m. p. 218° (Found: C, 61·9; H, 4·9; N, 7·9. $C_{19}H_{18}O_4N_2S$ requires C, 61·6; H, 4·9; N, 7·6%).

3-Methoxy-2-naphthaldehyde.—The above hydrazide (1 g.) in diethylene glycol (20 ml.) was heated and stirred at 160° during addition of anhydrous sodium carbonate (2·5 g.) and afterwards until the evolution of carbon dioxide had ceased. The mixture was cooled, diluted with water, and extracted with ether. Removal of the solvent from the dried extract gave a brownish-yellow gum which was purified by sublimation at 100°/1 mm. The *aldehyde* crystallised from light petroleum (b. p. 40—60°) in yellow rhombic plates (0·2 g.), m. p. 87—89° (Found: C, 77·2; H, 5·3. $C_{12}H_{10}O_2$ requires C, 77·4; H, 5·4%).

The *semicarbazone* was prepared from the aldehyde in the usual way, or more conveniently by the following modification of the McFadyen–Stevens reaction: the preceding hydrazide (30 g.) and semicarbazide hydrochloride (10 g.) were heated and stirred in diethylene glycol (600 ml.) at 160° until all had dissolved. After addition of anhydrous sodium carbonate (75 g.) stirring was continued for 20 min., until gas evolution had ceased. The pale yellow suspension was poured into water (5 l.), and the product collected and dried (21·5 g.). It crystallised from dioxan in colourless plates, m. p. 233—234° (Found: C, 64·2; H, 5·4; N, 16·8. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·3; N, 17·3%).

2-Methoxy-3-methylnaphthalene.—The above semicarbazone (2 g.) in a solution from sodium (1 g.) in ethyl alcohol (50 ml.) was heated at 190—200° for 18 hr. When cold, the mixture was extracted with ether and the extract was washed with 10% sodium hydroxide solution and water, and dried (Na_2SO_4). Removal of solvent gave a crystalline *product* (1·2 g.) which after distillation *in vacuo* crystallised from light petroleum (b. p. 40°) in plates, m. p. 74—75° (Found: C, 84·1; H, 7·0. $C_{12}H_{12}O$ requires C, 83·7; H, 7·0%). Acidification of the alkaline washings gave a substance which after isolation with ether crystallised from acetone–benzene in nacreous plates, m. p. 187—188° (Found: C, 75·8; H, 6·0%). It gave a positive ceric ammonium nitrate test for an alcoholic group and did not depress the m. p. of 3-hydroxymethyl-2-naphthol described below.

3-Hydroxymethyl-2-naphthol.—2-Hydroxy-3-naphthoic acid (9·45 g.) in dry ether (200 ml.) was added dropwise to lithium aluminium hydride (4·75 g.) in dry ether (150 ml.) stirred in a stream of nitrogen. After 1 hr. water (10 ml.) was cautiously added and the solution acidified with hydrochloric acid. After extraction with ether, the extract was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. The residual solid (8·5 g.), m. p. 185°, crystallised from ethyl alcohol in prismatic plates, m. p. 187—188° (Found: C, 76·0; H, 5·5. $C_{11}H_{10}O_2$ requires C, 75·9; H, 5·75%). The *di*-p-*nitrobenzoyl derivative* crystallised from acetone in needles, m. p. 169° (Found: C, 63·8; H, 3·5; N, 5·8. $C_{25}H_{16}O_8N_2$ requires C, 63·6; H, 3·4; N, 5·9%).

3-Methyl-2-naphthol.—2-Methoxy-3-methylnaphthalene (4·7 g.) was refluxed with acetic

XUM

acid (40 ml.) and hydrobromic acid (*d* 1·5; 15 ml.) for 4 hr. The cooled mixture was diluted with water and extracted with ether, and the ethereal solution washed with sodium hydrogen carbonate to remove acetic acid. The naphthol (2·1 g.) isolated by means of 10% aqueous sodium hydroxide crystallised from benzene–light petroleum (b. p. 40—60°), in plates, m. p. 159·5—160·5° (Found: C, 83·5; H, 6·2. $C_{11}H_{10}O$ requires C, 83·5; H, 6·3%).

3-Bromo-2-naphthol.—1 : 3-Dibromo-2-naphthol [9] (10 g.), acetic acid (60 ml.), hydriodic acid (*d* 1·7; 4 ml.), and a trace of red phosphorus were refluxed for 4 hr. The filtered solution was diluted with water and extracted with ether. After being washed with water and sodium hydrogen carbonate solution, the ethereal extract was dried (Na_2SO_4) and evaporated. 3-Bromo-2-naphthol (5·2 g.) crystallised from light petroleum (b. p. 40—60°) in colourless plates, m. p. 80—81° (Found: C, 53·7; H, 3·0. Calc. for $C_{10}H_7OBr$: C, 53·8; H, 3·1%). Clemo and Spence [5] give m. p. 80—81°.

3 : 4-Dihydro-3-oxonaphtho[2,3-*b*]-1 : 4-*oxazine.*—3-Amino-2-naphthol (3·2 g.) in ethyl alcohol (50 ml.) containing sodium (0·46 g.) was refluxed with ethyl bromoacetate (2·5 ml.) for 4 hr. After cooling, a solid [1·6 g.; m. p. 265° (decomp.)] was collected and the filtrate diluted with water and shaken with ether. The ethereal solution was washed successively with dilute sodium hydroxide, hydrochloric acid, and water, dried (Na_2SO_4), and evaporated, more solid (1 g.) being obtained. The combined crops of naphtho-oxazine crystallised from methyl alcohol in needles, m. p. 268° (decomp.) (Found: C, 72·3; H, 4·3; N, 7·2. Calc. for $C_{12}H_9O_2N$: C, 72·3; H, 4·5; N, 7·0%) (no aminonaphthyloxyacetic ester was obtained by basifying the acid washings). Fries, Walter, and Schilling [10] give m. p. 270°.

3-Cyano-2-methoxynaphthalene.—3-Amino-2-methoxynaphthalene (6·9 g.) in water (70 ml.) and concentrated hydrochloric acid (12 ml.) was stirred at 0—5° during the dropwise addition of sodium nitrite (3 g.) in water (10 ml.) and for a further 0·75 hr. This diazonium mixture was then added with stirring to a solution of potassium cuprocyanide (from 16 g. of copper sulphate and 16 g. of sodium cyanide) in water (100 ml.), the temperature being maintained at 70—80°, and the whole was steam-distilled. The distillate was extracted with ether, and the extract washed with dilute sulphuric acid, water, and dried (Na_2SO_4). Removal of the solvent gave the *cyanide* (4 g.) which after sublimation *in vacuo* had m. p. 125° (Found: C, 78·7; H, 5·0; N, 7·75. $C_{12}H_9ON$ requires C, 78·7; H, 4·9; N, 7·65%).

3-Cyano-2-naphthol.—3-Cyano-2-methoxynaphthalene (3·5 g.) and pyridine hydrochloride (12 g.) were heated in a sealed tube at 200° for 4 hr. After cooling, the contents were diluted with water, acidified with hydrochloric acid, and extracted with ether, and naphtholic material further extracted with dilute aqueous sodium hydroxide. Acidification of the alkaline extract and extraction with ether gave the *naphthol* (2·45 g.), m. p. 180°. It crystallised from aqueous ethyl alcohol in monoclinic prisms, m. p. 185° (Found: C, 78·3; H, 4·13; N, 8·3. Calc. for $C_{11}H_7ON$: C, 78·2; H, 4·15; N, 8·3%). Lesser, Kranepuhl, and Gad [11] give m. p. 188—189°.

3-Hydroxynaphthalene-2-carboxyamide.—(*a*) 3-Cyano-2-methoxynaphthalene (2·3 g.) in acetic acid (8 ml.) was refluxed with hydrobromic acid (*d* 1·5; 3 ml.) for 4 hr. The solution was poured into water and extracted with ether, and naphtholic material removed from the extract by alkali. The alkaline solution was acidified and extracted with ether, the extract dried (Na_2SO_4), and the solvent distilled off. The residual amide (1·2 g.) crystallised from aqueous methyl alcohol in prismatic plates, m. p. 215° (Found: C, 70·9; H, 5·2; N, 7·1. Calc. for $C_{11}H_9O_2N$: C, 70·6; H, 4·8; N, 7·4%). Fries [12] gives m. p. 217°. (*b*) Demethylation of 3-methoxynaphthalene-2-carboxyamide [6] by hydrobromic acid (*d* 1·5) as above gave the phenolic amide, m. p. 215°, undepressed on admixture with the product from (*a*) above.

2-Oxonaphtho[2,3-*b*]-1 : 4-*dioxan.*—3-Hydroxy-2-naphthyloxyacetic acid (0·5 g.) was refluxed with acetic anhydride (5 ml.) for 2 hr., the reagent distilled off, and the product sublimed at 120° (bath-temp.)/0·5 mm. The sublimate of *naphthodioxan*, crystallised from ethyl alcohol, benzene, or ether–light petroleum (b. p. 40—60°), had m. p. 142—143° (Found: C, 71·9; H, 3·9. $C_{12}H_8O_2$ requires C, 72·0; H, 4·0%). Repeated crystallisation of the sublimate from aqueous methyl alcohol gave a product, m. p. 89—92°, which was insoluble in sodium hydrogen carbonate solution and gave a red colour with *p*-nitrobenzenediazonium fluoroborate. It crystallised from ether–light petroleum (b. p. 60—80°) in colourless rectangular

[9] James and Woodcock, *J.*, 1951, 3418.
[10] Fries, Walter, and Schilling, *Annalen*, 1935, **516**, 248.
[11] Lesser, Kranepuhl, and Gad, *Ber.*, 1925, **58**, 2109.
[12] Fries, *ibid.*, p. 2845.

prisms, m. p. 93—94° (Found: C, 67·4; H, 5·2%), undepressed on admixture with methyl 3-hydroxy-2-naphthyloxyacetate prepared as below.

Methyl 3-Hydroxy-2-naphthyloxyacetate.—A solution of 3-hydroxy-2-naphthyloxyacetic acid in anhydrous ether was treated with ethereal diazomethane (1 equiv.). After 1 hr. the solution was washed with sodium hydrogen carbonate solution, dried, and evaporated. The residual *methyl ester* crystallised from ether–light petroleum (b. p. 60—80°) in prisms, m. p. 93—94° (Found: C, 67·05; H, 5·0. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%).

2 : 2-*Dimethyl*-3-*oxonaphtho*[2,3-*b*]-1 : 4-*dioxan.*—This *compound* was prepared for comparison with 2 : 3-dihydro-2-oxo-2′ : 3′-naphtho-1 : 4-dioxan. 2 : 3-Dihydroxynaphthalene (3·2 g.), in a solution from sodium (0·46 g.) in ethyl alcohol (30 ml.), was refluxed with ethyl α-bromo-α-methylpropionate (3 ml.) for 4 hr. and then for a further 1 hr. after the addition of excess of 10% aqueous sodium hydroxide. The solution was cooled and acidified with hydrochloric acid, and the *product* (1·5 g.) extracted with ether. It crystallised from ethyl alcohol in monoclinic prisms, m. p. 144—145° (Found: C, 73·5; H, 5·2. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%); it was insoluble in cold 10% aqueous sodium hydroxide but dissolved on gentle warming, acidification even with acetic acid re-forming the lactone.

α-(3-*Methoxy*-2-*naphthyloxy*)-α-*methylpropionic Acid.*—(*a*) 3-Methoxy-2-naphthol (0·9 g.), condensed with ethyl α-bromo-α-methylpropionate in the usual way, gave a *product* (0·6 g.) which crystallised from ether–light petroleum (b. p. 40—60°) in prisms, m. p. 105—106° (Found: C, 69·1; H, 6·1. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·15%). (*b*) A solution of 2 : 3-dihydro-2 : 3-dimethyl-3-oxo-2′ : 3′-naphtho-1 : 4-dioxan in a slight excess of warm 10% aqueous sodium hydroxide was treated dropwise with shaking with excess of dimethyl sulphate. The bicarbonate-soluble material was extracted with ether, the extract dried, and the ether distilled off. The product crystallised from aqueous methyl alcohol in prisms, m. p. 102—103° (Found: C, 69·0; H, 6·0%) undepressed on admixture with the product from (*a*). Refluxing with hydriodic acid (*d* 1·7) in acetic acid for 2 hr. gave 2 : 3-dihydro-2 : 2-dimethyl-3-oxo-2′ : 3′-naphtho-1 : 4-dioxan, m. p. and mixed m. p. 143—144°.

3-*Carboxy*-2-*naphthyloxyacetic acid.*—Ethyl 3-hydroxy-2-naphthoate (2·2 g.) was dissolved in a solution from sodium (0·23 g.) in ethyl alcohol (75 ml.) and refluxed with ethyl bromoacetate (1·2 ml.) for 8 hr. The solution was poured into water and extracted with ether, and unchanged naphtholic material removed by cold 0·1N-sodium hydroxide. After washing of the ethereal solution with water, the solvent was distilled off and the residue (1·86 g.) hydrolysed by refluxing 10% sodium hydroxide solution for 1 hr. The solution was then cooled, acidified, and extracted with ether, the ethereal solution washed with water and dried (Na_2SO_4), and the solvent removed. The *product* (1·1 g.) crystallised from ethyl alcohol or acetic acid in rhombic plates, m. p. 220—221°. Analytical details are given in the Table.

2 : 3-*Dihydro*-2-*oxonaphtho*[2,3-*b*]*oxazole.*—3-Hydroxy-2-naphthhydrazide (75 g.) in ethyl alcohol (1 l.) was cooled to 0° after addition of dry ethanolic hydrogen chloride (135 ml. containing 19·8 g. of hydrogen chloride). *iso*Pentyl nitrite (54 ml.) was added portionwise with stirring, which was continued for a further 2 hr. After refluxing until nitrogen evolution had ceased (0·5 hr.), the solution was concentrated to 200 ml. and poured into water (1 l.). The product was collected, washed with water, dried, and crystallised from ethyl alcohol (58·4 g.). Recrystallisation from ethyl alcohol–ether (charcoal) gave colourless needles, m. p. 200—201° (Found: C, 71·7; H, 3·9; N, 7·3. Calc. for $C_{11}H_7O_2N$: C, 71·4; H, 3·8; N, 7·6%). Fries [12] gives m. p. 205°.

3-*Iodo*-2-*naphthol.*—3-Amino-2-naphthol (7·95 g. prepared from the above oxazole by hydrolysis with 40% aqueous sodium hydroxide) in hot water (100 ml.) containing sulphuric acid (12 ml.) was stirred at 10—15° during the dropwise addition of a solution of sodium nitrite (3·45 g.) in water (30 ml.), and for a further 1 hour. Urea (10 g.) in water (20 ml.) was then added, followed by potassium iodide (25 g.) in water (60 ml.), and sulphuric acid (8 ml.) in water (20 ml.), and stirring continued for 1 hour. Steam-distillation of the tarry product and ether-extraction of the distillate gave crude 3-iodo-2-naphthol (2·25 g., 16·6%) which by sublimation gave colourless needles, m. p. 104°. Goldstein and Gardiol [6] reported a 12% yield, m. p. 105°.

Attempted Preparation of 3-*Iodo*-2-*naphthol using* n-*Propyl-lithium.*—A solution of *n*-propyl-lithium (prepared from 0·16 g. of lithium according to "Organic Reactions," Vol. VI, p. 352) in anhydrous ether (50 ml.) was added dropwise to a solution of 3-bromo-2-naphthol (1 g.) in dry ether (20 ml.) and the whole was stirred for 1 hr. in an atmosphere of nitrogen. Iodine (1 g.)

XUM

in ether (20 ml.) was added and stirring continued for 0·5 hr., followed by refluxing 0·5 hr. The cooled ethereal solution was washed with sodium thiosulphate solution, and naphtholic material extracted with alkali. Acidification of the alkaline solution and isolation with ether gave a gum which after sublimation was repeatedly crystallised from light petroleum (b. p. 40°) until chromatographically pure. The naphthol, m. p. 86—87°, gave an *oxyacetic acid*, m. p. 207—208° (Found: C, 35·1; H, 2·1%), which did not depress the m. p. of the authentic specimen prepared as below.

3-Bromo-1-iodo-2-naphthol.—This *naphthol* was prepared from 3-bromo-2-naphthol by Marsh's method.[13] After repeated fractional sublimation (to remove 3-bromo-2-naphthol) it crystallised from light petroleum (b. p. 40°) in prisms, m. p. 82—83° (Found: C, 34·3; H, 2·0. $C_{10}H_6OBrI$ requires C, 34·4; H, 1·7%). The *oxyacetic acid* crystallised from aqueous methyl alcohol in colourless monoclinic prisms, m. p. 207—208° (Found: C, 35·7; H, 2·1. $C_{12}H_8O_3BrI$ requires C, 35·45; H, 2·0%).

3-Substituted 2-naphthyloxyacetic Acids.—Of these only the 3-chloro-[9] and 3-hydroxy-[14] are known. The acids listed in the Table were prepared by the method described previously,[15] 3-methoxy- and 3-nitro-2-naphthol being obtained by published methods.[16]

The authors thank Mrs. V. W. Hilton for assistance with the experimental work and Mr. D. R. Clifford for the analyses.

Department of Agriculture & Horticulture, University of Bristol, Research Station, Long Ashton, Bristol. [*Received, August 12th*, 1958.]

[13] Marsh, *J.*, 1927, 3164.
[14] Shibata and Okuyama, *Bull. Chem. Soc. Japan*, 1936, **11**, 117.
[15] James and Woodcock, *J.*, 1951, 3418.
[16] Friedlander and Silberstern, *Monatsh.*, 1902, **23**, 513; Woodcock and Clifford, *J.*, 1957, 4139.

---

953. *Furan and Tetrahydrofuran Compounds Analogous to Ganglion-blocking Agents of the 3-Oxapentane-1 : 5-bistrialkylammonium Series.*

By E. W. Gill and H. R. Ing.

Quaternary halides from 2 : 5-bisdialkylaminomethyl-furan and -tetrahydrofuran, analogous to 3-oxapentane-1 : 5-bis(quaternary ammonium) salts that block ganglionic transmission, have been synthesized for testing as ganglion-blocking agents. Tetrahydro-5-methylfurfuryltrimethylammonium iodide and chloroaurate, stereoisomeric with the deoxymuscarine salts, and tetrahydro-5-hydroxymethylfurfuryltrimethylammonium iodide, an isomer of muscarine, have also been prepared.

In connexion with theoretical studies on the effect of inter-quaternary distance on the ganglion-blocking activity of bis(quaternary ammonium) salts [1] it was of interest to make compounds which would have rigid structures linking the two quaternary ammonium groups but would be analogues of highly active drugs with a flexible linking chain. In compounds with a rigid system the inter-quaternary distance could be defined within close limits, whereas for flexible molecules an inter-quaternary distance–probability distribution had to be calculated.

Fakstorp *et al.*[2] prepared a large series of 3-oxapentane-1 : 5-bis(quaternary ammonium) salts of which one of the most active was the unsymmetrically alkylated compound (I; R = H), which was about 1·5 times as active as hexamethonium. Replacement of the oxapentane chain by the 2 : 5-dimethylfuran or tetrahydro-2 : 5-dimethylfuran system would provide analogues of the oxapentane compounds with a rigid structure linking the two nitrogen atoms. Such compounds, particularly the tetrahydrofuran compounds, would be approximately isosteric with branched-chain oxapentane derivatives of type (I; R = Me) which are only slightly less active than the straight-chain compounds.[2]

[1] Gill, *Proc. Roy. Soc.*, *B*, in the press.
[2] Fakstorp, Pedersen, Poulsen, and Schilling, *Acta Pharmacol. Toxicol.*, 1957, **13**, 52.

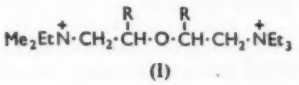
Moreover, 5-methylfurfuryltrimethylammonium is known to stimulate ganglia, being about one-quarter as effective as acetylcholine itself in the perfused superior cervical ganglion (cat),[3] so that the furan ring *per se* does not prevent the normal action of mono-quaternary trimethylammonium salts at the ganglionic synapse. Consequently any striking difference between the ganglion-blocking activity of the furan or tetrahydrofuran compounds and the oxapentane compounds could reasonably be attributed to the rigidity of the structure linking the two nitrogen atoms.

Bis(quaternary ammonium) furan compounds of the desired type were conveniently prepared from furfuryl alcohol. A Mannich condensation of furfuryl alcohol with a dialkylamine hydrochloride and paraformaldehyde gave a 5-dialkylaminomethylfurfuryl alcohol (III) which was quaternized with methyl or ethyl iodide; subsequent treatment of the corresponding quaternary chloride, first with thionyl chloride and then with a tertiary amine, gave the bisquaternary compound (II) which was isolated and purified as its 4 : 4′-diaminostilbene-2 : 2′-disulphonate [4] and then converted into the dibromide.

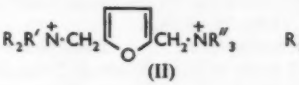
The structure of the Mannich condensation product (III) was proved by treating 5-chloromethylfurfuraldehyde,[5] of known structure,[6] with diethylamine and reducing the product with aluminium *iso*propoxide to 5-diethylaminomethylfurfuryl alcohol, identical with the Mannich condensation product when diethylamine hydrochloride was used.

Catalytic reduction of 5-dimethylaminomethylfurfuryl alcohol over Raney nickel gave 5-dimethylaminomethyltetrahydrofurfuryl alcohol (IV); a nine-stage synthesis of this compound from dibromoadipic acid has been reported recently.[7] The methiodide of (IV) is an isomer of muscarine iodide (V), but is pharmacologically inert, as is 5-hydroxymethylfurfuryltrimethylammonium iodide.[3] 5-Dimethylaminomethyltetrahydro-2-methylfuran was also prepared in a similar way from 2-methylfuran. Its methiodide, presumably the *cis*-(±)-isomer,[8] had the same R_F value as deoxymuscarine (VI), prepared from muscarine,[9] but the m. p. of the chloroaurate differed from that of deoxymuscarine.

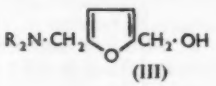
An attempt was made to prepare bisquaternary tetrahydrofuran compounds in the



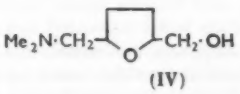
(I)



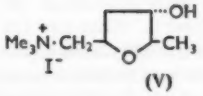
(II)



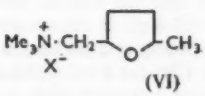
(III)



(IV)



(V)



(VI)

same way as the furan compounds, by using tetrahydrohydroxymethylfurfurylamines, but this was unsuccessful. Furfurylamines, prepared from furfuraldehyde by the Leuckart reaction,[10] do not undergo the Mannich condensation under normal conditions, but 2 : 5-bisdialkylaminomethylfurans can be obtained in variable yields under more drastic conditions. Catalytic reduction and quaternization then yielded the desired bisquaternary tetrahydrofurans.

Both the furan and the tetrahydrofuran bisquaternary ammonium compounds were inactive as ganglion-blocking agents, a result which proved to be consistent with the conclusions of the theoretical studies already mentioned.[1]

[3] Ing, Kordik, and Tudor-Williams, *Brit. J. Pharmacol.*, 1952, **7**, 103.
[4] Leeds and Slack, *J.*, 1956, 3941.
[5] Fischer and Neyman, *Ber.*, 1914, **47**, 973.
[6] Fenton and Gostling, *J.*, 1901, 807.
[7] Gryszkiewicz-Trochimowski, Gryszkiewicz-Trochimowski, and Levy, *Bull. Soc. chim. France*, 1958, 603.
[8] Wiggins and Wood, *J.*, 1950, 1566.
[9] Kögl, Salemink, Schouten, and Jellinek, *Rec. Trav. chim.*, 1957, **76**, 126.
[10] Weilmuenster and Jordan, *J. Amer. Chem. Soc.*, 1945, **67**, 415.

XUM

Experimental

5-Dialkylaminofurfuryl Alcohols.—Equimolar amounts of furfuryl alcohol and dialkylamine hydrochloride in ethanol were boiled under reflux with paraformaldehyde (1·5 mol.) for 2 hr. One mol. of paraformaldehyde was then added and heating continued for 12 hr. The solvent was removed *in vacuo* and a concentrated aqueous solution of the residue made strongly alkaline with sodium hydroxide and extracted with ether. After being dried (Na_2SO_4) the ethereal extract was distilled. 5-Dimethylaminomethylfurfuryl alcohol had b. p. 125—135°/15 mm., n_D^{20} 1·4900 (yield 70%) (Found: C, 62·1; H, 8·5. Calc. for $C_8H_{13}O_2N$: C, 62·0; H, 8·4%). Its methiodide, crystallized from ethanol, had m. p. 128° as recorded by Ing *et al.*,[3] and its *ethiodide*, crystallized from ethanol–ethyl acetate, m. p. 82° (Found: C, 38·4; H, 5·8; N, 4·6. $C_{10}H_{18}O_2NI$ requires C, 38·6; H, 5·8; N, 4·5%).

5-Diethylaminomethylfurfuryl alcohol had b. p. 140—146°/15 mm. (yield 60%) (Found: C, 65·1; H, 9·0. $C_{10}H_{17}O_2N$ requires C, 65·6; H, 9·3%). Its *methiodide*, crystallized from ethanol–ethyl acetate, had m. p. 68° (Found: C, 40·3; H, 6·2; N, 4·2. $C_{11}H_{20}O_2NI$ requires C, 40·6; H, 6·2; N, 4·3%). The orientation of these compounds was proved as follows: Diethylamine (13·2 g.) was added to 5-chloromethylfurfuraldehyde [5] (13 g.) in anhydrous ether (30 ml.). The solution was chilled occasionally during 2 hr. in order to moderate the reaction, then left overnight at room temperature. Precipitated diethylamine hydrochloride was removed and 5-diethylaminomethylfurfuraldehyde (60%) isolated by distillation; this had b. p. 128—130°/15 mm. It formed a yellow oil, darkening in air and too unstable to give satisfactory analyses; its *picrate*, m. p. 101—102°, crystallized from ethanol (Found: C, 46·7; H, 4·6; N, 13·3. $C_{16}H_{18}O_9N_4$ requires C, 46·8; H, 4·4; N, 13·7%).

This aldehyde (15 g.) was reduced by slow distillation through a column of its solution in propan-2-ol (150 ml.) containing aluminium *iso*propoxide, prepared from aluminium (0·38 g.), mercuric chloride (0·05 g.), and propan-2-ol (10 ml.). When no more acetone could be detected in the distillate (24 hr.) the solvent was distilled off, the residue dissolved in water (50 ml.), and its aqueous solution basified strongly and extracted with ether. The dried extract (Na_2SO_4) gave 5-diethylaminomethylfurfuryl alcohol (11·3 g., 75%), b. p. 142—146°/15 mm., whose *α-naphthylurethane*, crystallized from light petroleum, had m. p. 104° alone or mixed with the α-naphthylurethane prepared from the Mannich condensation product (Found: C, 72·0; H, 6·6. $C_{21}H_{24}O_3N_2$ requires C, 71·6; H, 6·8%).

2 : 5-Bisdialkylaminomethylfuran Dialkylobromides.—5-Dimethylaminomethylfurfuryl alcohol methiodide (29·7 g.) in methanol (100 ml.) was heated under reflux with freshly prepared silver chloride (17·2 g.) for 2 hr. The filtrate from silver halides was evaporated to dryness *in vacuo*, and the residue covered with chloroform (20 ml.) and treated slowly with thionyl chloride (13·3 g.) in chloroform (20 ml.). Next day the solution was evaporated *in vacuo* and the dark brown residue heated with trimethylamine (40 ml.; 33% w/w in ethanol) in a pressure bottle at 100° for 4 hr. The solvent was removed *in vacuo*, and the residue taken up in water (100 ml.) and treated with sodium 4 : 4′-diaminostilbene-2 : 2′-disulphonate (41·1 g.) in water (100 ml.) at 40°. The precipitated amsonate was collected after the mixture had been stored overnight at 0° and recrystallized from water (yield 35 g., 60%). The amsonate (17·4 g.) was suspended in water (75 ml.) at 50°, treated with hydrobromic acid (7·5 ml.; *d* 1·46), stirred, and chilled. The amsonic acid was recovered and washed with warm water (20 ml.), and the filtrate evaporated to dryness *in vacuo*. Three crystallizations of the residue from ethanol–ethyl acetate gave *2 : 5-bisdimethylaminomethylfuran dimethobromide*, m. p. 238° (decomp.) (10 g., 90%) (Found: C, 39·0; H, 6·65; N, 7·5. $C_{12}H_{24}ON_2Br_2$ requires C, 38·7; H, 6·45; N, 7·5%).

Similarly were prepared: *2-Diethylaminomethyl-5-dimethylaminomethylfuran diethobromide*, m. p. 234° (decomp.) (Found: C, 44·35; H, 7·3; N, 6·4. $C_{16}H_{32}ON_2Br_2$ requires C, 44·85; H, 7·5; N, 6·55%). *2-Diethylaminomethyl-5-ethylmethylaminomethylfuran diethobromide*, m. p. 228° (decomp.) (Found: C, 46·5; H, 7·7; N, 6·4. $C_{17}H_{34}ON_2Br_2$ requires C, 46·2; H, 7·7; N, 6·4%).

2-Dimethylaminomethyltetrahydrofurfuryl Alcohol.—2-Dimethylaminomethylfurfuryl alcohol (25·2 g.) in ethanol (100 ml.) was hydrogenated over Raney nickel W7 [11] at room temperature and 100 atm. The product (21 g., 80%) had b. p. 120—122°/15 mm., n_D^{20} 1·4640 (Found: C, 60·7; H, 10·6; N, 8·7. Calc. for $C_8H_{17}O_2N$: C, 60·3; H, 10·7; N, 8·8%). The *picrate*,

[11] Adkins and Billica, *J. Amer. Chem. Soc.*, **1948**, **70**, 695.

crystallized from ethanol, had m. p. 102° (Found: C, 43·0; H, 5·0. $C_{14}H_{20}O_9N_4$ requires C, 43·3; H, 5·2%). The methiodide had m. p. 85° (Gryszkiewicz-Trochimowski *et al.*[7] record m. p. 83—84°).

2-Dimethylaminomethyltetrahydro-5-methylfuran.—2-Dimethylaminomethyl-5-methylfuran [12] was hydrogenated in the same way and the tetrahydrofuran derivative obtained in 70% yield; it had b. p. 163°/760 mm., n_D^{20} 1·4358 (Found: C, 67·3; H, 11·8; N, 9·4. Calc. for $C_8H_{17}ON$: C, 67·2; H, 11·9; N, 9·8%). The methiodide, prepared in acetone solution, had m. p. 157° and R_F 0·68 when chromatographed on Whatman No. 1 (solvent system: butanol 5, ethanol 5, water 2). Kögl *et al.*[9] report R_F 0·65—0·68 for deoxymuscarine. The methochloroaurate, crystallized from water, had m. p. 132° whereas Kögl *et al.*[9] record m. p. 108—109° for deoxymuscarine chloroaurate.

2 : 5-Bisdialkylaminomethylfurans.—*NN*-Dimethylfurfurylamine [10] (25 g.), dimethylamine hydrochloride (20 g.), and paraformaldehyde (9 g.) in propan-1-ol (100 ml.) were boiled under reflux for 5 hr., more paraformaldehyde (6 g.) being added after 1·5 and 3 hr. The residue after removal of solvent *in vacuo* was taken up in water, and the solution made strongly alkaline and extracted with ether. Fractionation of the dried extract (Na_2SO_4) gave unchanged furfuryldimethylamine (14·4 g.; b. p. 60—130°/20 mm.) and *2 : 5-bisdimethylaminomethylfuran*, b. p. 140—150°/20 mm. (10·5 g., 72% on unrecovered furfuryldimethylamine) (Found: C, 65·6; H, 9·75; N, 15·2. $C_{10}H_{18}ON_2$ requires C, 65·9; H, 9·9; N, 15·4%).

2-Diethylaminomethyl-5-dimethylaminomethylfuran, obtained (30%) in the same way from furfuryldiethylamine,[10] had b. p. 128—130°/15 mm. (Found: C, 68·4; H, 10·3; N, 13·1. $C_{12}H_{22}ON_2$ requires C, 68·6; H, 10·5; N, 13·3%).

2 : 5-Bisdialkylaminomethyltetrahydrofurans and their dialkyloiodides.

NN'-Alkylation	M. p. or b. p./mm.	Found (%) C	H	N	I	Required (%) C	H	N	I
NNN'N'-Tetramethyl	122—124°/15 mm.	64·5	11·65	14·9	—	64·5	11·8	15·1	—
,, ,, dipicrate [a]	187—188°	—	—	—	—	—	—	—	—
,, ,, dimethiodide [b]	>300°	30·8	6·1	—	54·3	30·7	6·0	—	54·1
,, ,, diethiodide [c]	165°	34·0	6·6	—	50·8	33·7	6·4	—	51·0
NN-Dimethyl-*N'N'*-diethyl	124—126°/15 mm.	67·0	12·0	12·9	—	67·4	12·1	13·1	—
,, ,, dimethiodide [a]	>300°	33·5	6·4	—	50·8	33·7	6·4	—	51·0
,, ,, diethiodide [a]	185°	36·3	6·9	—	48·4	36·5	6·8	—	48·3

Solvents for crystallization: [a] water; [b] 1 : 9 v/v aqueous methanol; [c] ethanol–ethyl acetate.

2 : 5-Bisdialkylaminomethyltetrahydrofurans.—The 2 : 5-bisdialkylaminomethylfuran (0·1 mole) in ethanol (100 ml.) was hydrogenated over Raney nickel W7 at 20°/100 atm. Hydrogen uptake ceased after about 1 hr. The catalyst was removed by centrifugation and the supernatant solution fractionated. Yields were about 70%. Analyses for these *compounds* and their *meth-* and *eth-iodides* are given in the Table.

We thank the Medical Research Council for a Scholarship (to E. W. G.).

DEPARTMENT OF PHARMACOLOGY, OXFORD. [*Received, August 20th*, 1958.]

[12] Holdren and Hixon, *J. Amer. Chem. Soc.*, 1946, **68**, 1198.

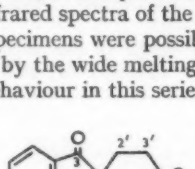
XUM

954. *The Preparation of (±)-α- and (±)-β-Grisan-3 : 4′-diol and the Resolution of the α-Isomer.*

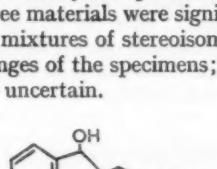
By P. McCloskey.

Stepwise reduction of grisan-3 : 4′-dione with sodium borohydride has yielded (±)-α- and (±)-β-grisan-3 : 4′-diol by way of α- and β-4′-hydroxygrisan-3-ones. The (±)-α-diol has been resolved into optical antipodes and the (+)-α- and the (+)-β-diol have been shown to be metabolites of grisan-3 : 4′-dione in the broad bean (*Vicia faba* L.).

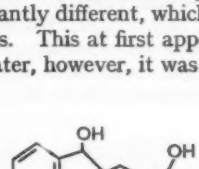
In studies[1] on the translocation of certain grisan derivatives in the broad bean (*Vicia faba* L.), a crystalline dextrorotatory grisan-3 : 4′-diol (cf. II, III) was isolated from the shoots of plants which had been grown for several days in a dilute aqueous solution of grisan-3 : 4′-dione (I). A diol of identical ultraviolet absorption and similar optical rotation was isolated from the residual solution used for growth (from which all the dione had disappeared) and, in low yield sufficient only for spectral examination, from the plant roots, but the infrared spectra of the three materials were significantly different, which suggested that the specimens were possibly mixtures of stereoisomers. This at first appeared to be supported by the wide melting ranges of the specimens; later, however, it was found that melting behaviour in this series is uncertain.



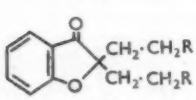
(I)



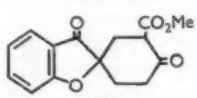
(II)



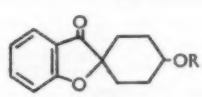
(III)



(IV)



(V)



(VI)

Conversion of grisan-3 : 4′-dione (I) into the diol introduces an asymmetric centre at position 3, and the possibility of geometrical isomerism at position 4′ (the molecule has a plane of symmetry through this second centre). The 4′-hydroxyl group may thus be *trans* or *cis* to the 2 : 3-bond, and since this bond will be equatorial in the preferred conformation the most probable structures for the stable (α) and less stable (β) form of (±)-grisan-3 : 4′-diol are (II) and (III) in which the 4′-hydroxyl group is equatorial and axial respectively.

Grisan-3 : 4′-diol was obtained as a mixture of stereoisomers by reduction of grisan-3 : 4′-dione (I) which had been synthesised by dicyanoethylation of coumaranone, conversion of the dicyano-compound (IV; R = CN) into the dimethyl ester (IV; R = CO_2Me) by treatment with methanolic hydrochloric acid, Dieckmann cyclisation of this ester, and acid hydrolysis of the β-keto-ester (V).

Reduction of grisan-3 : 4′-dione with lithium aluminium hydride yielded a solid mixture of isomeric diols which, as transpired, contained a large proportion of the α-isomer but was not readily separated into the components by fractional crystallisation or chromatography on alumina. Both processes were difficult to follow because the material crystallised poorly, yielding solids of ill-defined melting behaviour. However, the diol mixture was oxidised selectively at the 3-position by chromic oxide–pyridine, giving in high yield a mixture of the 4′-hydroxygrisan-3-ones (VI; R = H) as indicated by the ultraviolet absorption [$\lambda_{max.}$ 250, 325 mμ (log ε 4·0, 3·7)] [the diol has $\lambda_{max.}$ 281, 288 mμ (log ε 3·5, 3·4)]. The glassy product did not crystallise but was separated into two different ketols by fractional crystallisation of the 3 : 5-dinitrobenzoates. Hydrolysis of these derivatives afforded

[1] Crowdy, Green, Grove, McCloskey, and Morrison, *Biochem. J.*, in the press.

the pure ketols, the main product, considered to be that derived from the α-diol, being termed α and the minor β; both ketols then crystallised readily.

These ketols were more satisfactorily prepared by selective partial reduction of grisan-3 : 4′-dione with sodium borohydride. In ice-cold aqueous methanol the 4′-carbonyl group could be virtually titrated with aqueous sodium borohydride whereas reduction of the 3-carbonyl group was relatively slow under these conditions. Crystallisation of the product gave almost pure α-ketol and a residue from which, after conversion into the mixed dinitrobenzoates, the pure β-derivative was separated by fractional crystallisation. By this procedure the α- and the β-ketol were obtained in yields of 85% and 8% respectively, a ratio of stable to less stable forms rather higher than that previously obtained from unhindered *cyclo*hexanones by reduction with sodium borohydride in aqueous methanol.[2,3]

Reduction of the α-ketol with excess of borohydride gave (±)-α-grisan-3 : 4′-diol, regarded as (II), which appeared to crystallise as a racemic mixture since its infrared spectrum (solid) was identical with that of the optically active material isolated from the bean shoots. This result, which suggested that the natural product might be pure (+)-α-grisan-3 : 4′-diol, was fortunate as it was impossible to compare the spectra in solution because of the slight solubility of the diols in all the useful spectral solvents.

Attempts to resolve the inactive α-diol into optical antipodes were at first unsuccessful, *e.g.*, by chromatography of the diol on a relatively large column of " activated " D-lactose,[4] chromatography of the oily bis-(−)-menthyloxyacetates on alumina, and preparation of salts of the hydrogen phthalates and 3-nitrophthalates with active bases. The last method, in which an attempt was made to confine esterification to the relatively unhindered 4′-position by the use of one equivalent of phthalic anhydride and to inhibit polymerisation by the choice of pyridine as solvent,[5] gave only ill-defined and mostly gummy derivatives.

It seemed that resolution employing fractional crystallisation was more likely to succeed if the diastereoisomeric mono-derivatives of the diol could be obtained uncontaminated with bis-derivatives. This was done by preparing the α-4′-(−)-*N*-menthylphthalamic ester [6] [VI; R = CO·C_6H_4·CO·NH-(−)-menthyl] and reducing the keto-group of this well-defined crystalline compound by sodium borohydride, though this led to some cleavage of the ester linkage. Fractional crystallisation, etc., of the resultant mixture of diastereoisomeric α-3-hydroxygrisan-4′-yl (−)-*N*-menthylphthalamates gave the pure (+)- and (−)-diastereoisomers (see p. 4736 for details), and hydrolysis yielded (+)- and (−)-α-grisan-3 : 4′-diols (II), having $[\alpha]_D$ ±73° in reasonable agreement with that of the natural diol obtained from the plant shoots ($[\alpha]_D$ + 79° in a determination using 1·5 mg.).[1] Both enantiomorphs melted at *ca.* 205°, a value retained by the (−)-isomer on rapid recrystallisation from benzene–acetone; in general, however, attempts to recrystallise this high-melting modification led to a crystalline product which melted much lower, over a wide range, possibly owing to a combination of polymorphism and the formation of viscous melts.

Reduction of the β-ketol with borohydride gave (±)-β-grisan-3 : 4′-diol, regarded as (III), which was not resolved. Infrared examination of the inactive diol, which also apparently crystallised as a conglomerate, indicated that this product was present in the natural diol isolated from the bean roots and from the residual treating solution, and it was then shown that a synthetic mixture containing almost equal quantities of the (±)-α- and (±)-β-diol had an infrared spectrum virtually identical with that of the natural diol from these two sources. This fact, considered together with the specific rotation of the material obtained from the residual treating solution ($[\alpha]_D$ + 68·5°),[1] leaves little doubt that the diols present in the mixture are both dextrorotatory.

[2] Dauben, Fonken, and Noyce, *J. Amer. Chem. Soc.*, 1956, **78**, 2579.
[3] Beckett, Harper, Balon, and Watts, *Chem. and Ind.*, 1957, 663.
[4] Prelog and Wieland, *Helv. Chim. Acta*, 1944, **27**, 1132.
[5] Levene and Mikeska, *J. Biol. Chem.*, 1927, **75**, 587.
[6] Human and Mills, *J.*, 1949, S 77.

XUM

Experimental

M. p.s are corrected unless otherwise stated. Microanalyses are by Messrs. W. Brown and A. G. Olney, of these laboratories, and R. Rothwell (Imperial Chemical Industries Limited, Dyestuffs Division).

The preparations leading to grisan-3 : 4′-dione were carried out in collaboration with Dr. J. R. Bartels-Keith, of these laboratories, and Dr. W. H. Davies (Imperial Chemical Industries Limited, Dyestuffs Division).

2 : 2-*Di*-2′-*cyanoethylcoumaranone*.—Coumaranone [7] (13·4 g.) and potassium *tert.*-butoxide (1·1 g.) in dioxan (30 ml.) were stirred vigorously at 15—23° during addition (20 min.) of acrylonitrile (10·6 g.). Stirring was continued for 5 hr. and the mixture then acidified with 2N-hydrochloric acid (5 ml.), poured into water (100 ml.), and extracted with ether. Concentration of the extract afforded prisms of 2 : 2-*di*-2′-*cyanoethylcoumaranone* (10·6 g.), having m. p. 83·5—84·5° after recrystallisation from ether (Found: C, 70·1; H, 5·4; N, 11·5. $C_{14}H_{12}O_2N_2$ requires C, 70·0; H, 5·0; N, 11·7%).

Chromatography on alumina in benzene–methanol (99 : 1) of the residual red gum obtained by evaporation of the mother-liquor yielded a further quantity (0·7 g.) of product, eluted as a pink band fluorescing blue in ultraviolet light.

Boiling the dinitrile with 5N-sodium hydroxide for 2½ hr. yielded 2 : 2-*di*-2′-*carboxyethylcoumaranone*, m. p. 137—138° (from water) (Found: C, 60·45; H, 5·1. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·0%). The *diethyl ester*, obtained by heating the acid in ethanol containing sulphuric acid (6% w/w), formed crystals, m. p. 27—28°, from ether (Found: C, 64·8; H, 6·55. $C_{18}H_{22}O_6$ requires C, 64·7; H, 6·6%).

2 : 2-*Di*-(2-*methoxycarbonylethyl*)*coumaranone*.—A mixture of 2 : 2-di-2′-cyanoethylcoumaranone (59·1 g.) in water (9 ml.), and methanol (250 ml.) saturated with hydrogen chloride, was set aside at room temperature for 2 hr. (protected against atmospheric moisture) and then heated at 60°. After 45 min. the precipitate of ammonium chloride was filtered off and washed with dry methanol. The combined filtrate and washings were boiled under reflux for 2½ hr., set aside at room temperature overnight, poured into water (1 l.), and extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate, dried, and evaporated and the product was twice distilled, to yield 2 : 2-*di*-(2-*methoxycarbonylethyl*)*coumaranone* (63·5 g.), b. p. 166—168°/0·4 mm. (Found: C, 62·9; H, 5·9. $C_{16}H_{18}O_6$ requires C, 62·7; H, 5·9%). Continuous extraction with ether of the aqueous mother-liquor afforded a further quantity (4·4 g.) of the crude ester.

Methyl (±)-3 : 4′-*Dioxograsan*-3′-*carboxylate*.—Sodium (3·85 g.) was powdered in dry toluene (300 ml.) and 2 : 2-di-(2-methoxycarbonylethyl)coumaranone (43·5 g.) in toluene (160 ml.) containing methanol (0·5 ml.) added with vigorous stirring during 1 hr., the mixture being heated to boiling during 30 min. After an initial lag the sodium was rapidly consumed and replaced by a yellowish-brown powder in a reaction which reached maximum velocity towards the end of the addition period, at which point heating was withdrawn for several min. A further portion of toluene (100 ml.) was added, and stirring and heating were continued for 11 hr., after which the mixture was set aside overnight, then poured into water (500 ml.) containing 2N-sulphuric acid (85 ml.) and extracted with ether. The extract was washed with sodium hydrogen carbonate solution, dried, and evaporated to a yellowish solid (35·8 g.), m. p. 117—123°. Crystallisation from light petroleum (b. p. 40—60°)–ether (2 : 1) yielded prisms of the *grisan ester*, m. p. 122·5—124° (Found: C, 65·85; H, 5·1. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·15%).

Grisan-3 : 4′-*dione*.—The above β-keto-ester (31·55 g.) was heated under reflux with dioxan (80 ml.), water (80 ml.), and concentrated hydrochloric acid (80 ml.), nitrogen being passed through the mixture and the exit gases occasionally tested for carbon dioxide (barium hydroxide). Evolution of carbon dioxide being negligible after 7 hr., the mixture was cooled and extracted with ether, and the extract washed with water and sodium hydrogen carbonate solution, dried, and evaporated to yield an orange gum (24·2 g.) which readily solidified. The combined crude product (43·5 g.) from several experiments was crystallised from ether, yielding prisms of *grisan*-3 : 4′-*dione* (16·4 g.), m. p. 89·5—90·5° (Found: C, 72·35; H, 5·65. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%), $\lambda_{max.}$ (in ethanol) 250, 328 mμ (log ε 4·0, 3·7). Evaporation of the mother-liquor and distillation of the gummy residue (b. p. 128—129°/0·5 mm.) gave an oil which afforded a further quantity (18 g.) of crystalline product, m. p. 89—90·5° (from ether). The

[7] Fries and Pfaffendorf, *Ber.*, 1910, **43**, 214; Mameli, *Gazzetta*, 1926, **56**, 759.

2 : 4-*dinitrophenylhydrazone* had m. p. 230—231° (from dioxan–ethanol) (Found: C, 57·75; H, 4·2; N, 14·1. $C_{19}H_{16}O_6N_4$ requires C, 57·6; H, 4·0; N, 14·15%).

Reduction of Grisan-3 : 4′-dione with Lithium Aluminium Hydride.—Grisan-3 : 4′-dione (5·4 g.) in dry ether (250 ml.) was stirred vigorously under reflux and treated with lithium aluminium hydride (1 g.) in four portions added at intervals of 15 min. After 3½ hr. the mixture was cooled at 0°, treated with ice until the excess of reagent had been decomposed, and then shaken with N-hydrochloric acid (175 ml.) and more ether (total ca. 1 l.) until all the solid had dissolved. After separation the ether solution was washed with saturated aqueous sodium hydrogen carbonate (10 ml.), dried, and evaporated, yielding a slightly gummy solid (5·44 g.). The ether-washed product (4·52 g.), a mixture of (±)-α- and (±)-β-grisan-3 : 4′-diol in which the former predominated as shown by infrared absorption, had m. p. 167—174°.

α- *and* β-4′-*Hydroxygrisan*-3-*one.*—(a) *By reduction of grisan*-3 : 4′-*dione.* Grisan-3 : 4′-dione (3·48 g.) in methanol (20 ml.) at 0° was treated dropwise with sodium borohydride (81%; 0·25 g.) in water (to 10 ml.). The reagent was at first rapidly consumed but after 7·55 ml. of the solution (equivalent to slightly more than that required for the reduction of one carbonyl group) had been added during 20 min. the excess of borohydride was sufficient to bleach a weak alcoholic solution of magenta in *ca.* 1 min. and persisted for a further 10 min. (at 0°) but had disappeared after 15 min. The mixture was then diluted with water and extracted with ether. Recovery gave a gum (3·47 g.) which readily crystallised when warmed with a little ether. Fractional crystallisation of the product, first from ether, and later from ether containing increasing quantities of light petroleum (b. p. 40—60°), yielded α-4′-*hydroxygrisan*-3-*one* (2·68 g.), m. p. 105·5—106·5° after further recrystallisation from ether (Found: C, 71·2; H, 6·4. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·5%), $\lambda_{max.}$ (in ethanol) 249, 324·5 mμ (log ε 3·98, 3·70). The 3 : 5-*dinitrobenzoate* crystallised as needles, m. p. 221—222°, from acetone (Found: C, 58·1; H, 4·2; N, 6·8. $C_{20}H_{16}O_8N_2$ requires C, 58·25; H, 3·9; N, 6·8%). The α-*naphthylurethane* formed needles, m. p. 176—177°, from ethanol (Found: C, 73·9; H, 5·4; N, 3·6. $C_{24}H_{21}O_4N$ requires C, 74·4; H, 5·5; N, 3·6%). The *acetyl derivative* formed leaflets, m. p. 132—133°, from light petroleum (b. p. 40—60°)–ether (1 : 1) (Found: C, 69·4; H, 6·2. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%).

The mother-liquor was evaporated and the gummy residue (0·78 g.) in dry benzene (10 ml.) and pyridine (1 ml.) was treated with 3 : 5-dinitrobenzoyl chloride (0·9 g.) in benzene (5 ml.) during 5 min. with shaking. The mixture was warmed on the water-bath for 30 min., then cooled and diluted with benzene and water. The benzene layer was washed, dried, and evaporated, yielding a slightly gummy solid (1·25 g.). Crystallisation from benzene (20 ml.) yielded β-3-*oxogrisan*-4′-*yl* 3 : 5-*dinitrobenzoate* (0·33 g.) as needles having m. p. 262—263° after further crystallisation from benzene (Found: C, 58·5; H, 4·3; N, 6·8. $C_{20}H_{16}O_8N_2$ requires C, 58·25; H, 3·9; N, 6·8%). Continued fractional crystallisation of the dinitrobenzoate mixture from benzene, and later from acetone, afforded the α-dinitrobenzoate (0·56 g.) and a further quantity of the β-dinitrobenzoate (0·2 g.).

The β-dinitrobenzoate (1·27 g.) was heated under reflux with potassium hydroxide (0·365 g.) in methanol (10 ml.) for 1 hr., then diluted with water (100 ml.) and extracted with ether (6 × 100 ml.). Recovery gave a gum (0·68 g.) which crystallised from ether yielding prisms of β-4′-*hydroxygrisan*-3-*one*, m. p. *ca.* 66—85° raised to 88·5—89·5° after 3 hours' heating at 78°/0·1 mm. followed by ½ hr. at 95—100°/0·1 mm. (Found, after heating: C, 71·6; H, 6·5. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·5%), $\lambda_{max.}$ (in ethanol) 249, 325 mμ (log ε 3·97, 3·70). The *acetyl derivative* formed prisms, m. p. 145—146°, from light petroleum (b. p. 40—60°)–ether (1 : 1) (Found: C, 69·5; H, 6·2. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%).

(b) *By oxidation of grisan*-3 : 4′-*diol.* Grisan-3 : 4′-diol (2·2 g.; mixture of isomers obtained by reduction of grisan-3 : 4′-dione with lithium aluminium hydride) was added rapidly with shaking to a suspension of the complex prepared from chromium trioxide (2·0 g.) in pyridine (20 ml.). After being shaken for 10 min. whilst the temperature rose slightly and the suspended complex was replaced by a brown amorphous powder, the mixture was set aside for 22 hr., then diluted with water and extracted with ether (6 × 125 ml.). The extract was washed with 2N-hydrochloric acid and saturated aqueous sodium hydrogen carbonate, dried, and evaporated to a glass (2·1 g.) which crystallised rapidly when seeded with α-4′-hydroxygrisan-3-one. Crystallisation from ether afforded α-4′-hydroxygrisan-3-one (0·72 g.) and a gummy residue which was converted into dinitrobenzoate and worked up as under (*a*), eventually yielding α-3-oxogrisan-4′-yl 3 : 5-dinitrobenzoate (1 g.), m. p. 216—218°, the β-derivative (0·27 g.), m. p. 259—261° after further crystallisation, and a mixture (0·5 g.) containing both derivatives.

XUM

(±)-α-*Grisan*-3 : 4′-*diol*.—α-4′-Hydroxygrisan-3-one (5·3 g.) in methanol (10 ml.) at 0° was treated with sodium borohydride (81%; 0·7 g.) in water (3 ml.). In a few minutes the mixture became warm and crystals were deposited. After being kept overnight at 0° the mixture was filtered and the solid rinsed with cold methanol and ether, affording (±)-α-*grisan*-3 : 4′-*diol* (4·77 g.), m. p. 175·5—180·5°, softening at 171° (Found: C, 71·3; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%), $\lambda_{max.}$ (in ethanol) 281, 288 mμ (log ε 3·49, 3·44). Dilution of the filtrate with water, extraction with ether, and recovery gave a further quantity (0·51 g.) of product, m. p. 169—173°, softening at 141°. Recrystallisation of the first crop afforded balls of opaque solid, m. p. 148—158° (cloudy melt), from benzene, or, from methanol, prisms which softened slowly above 171°, became partially opaque on continued heating, and gave a clear melt at 199°.

α-3-*Oxogrisan*-4′-*yl* (−)-N-*Menthylphthalamate*.—α-4′-Hydroxygrisan-3-one (2·18 g.) and phthalic anhydride (1·48 g.) were heated in dry pyridine (5 ml.) on the steam-bath for 4 hr. The mixture was cooled, diluted with cold N-hydrochloric acid, and extracted with ether. The extract was washed with 18% hydrochloric acid (3 × 10 ml.) and water (3 × 10 ml.), dried, and evaporated to a gum (3·67 g.). This product in dry benzene (5 ml.) was treated with freshly purified thionyl chloride (1·3 g.) in benzene (5 ml.), and the mixture set aside overnight at room temperature, then refluxed for 15 min. and evaporated under reduced pressure, affording a gum (3·8 g.) which was at once redissolved in benzene (5 ml.) and treated with pyridine (1 ml.) in benzene (2 ml.) followed by (−)-menthylamine (1·7 g.) in benzene (3 ml.). On addition of the base the mixture became warm and crystals were deposited. The mixture was set aside for 3 hr., then refluxed for 15 min., cooled, diluted with benzene, and shaken successively with 2N-hydrochloric acid, water, and saturated aqueous sodium hydrogen carbonate, dried, and evaporated, to yield a slightly gummy solid (4·5 g.). Recrystallisation from benzene (15 ml.) afforded pale yellow crystals (3·6 g.) of α-3-*oxogrisan*-4′-*yl* (−)-N-*menthylphthalamate*, $[\alpha]_D$ −29° (*c* 1·12 in ethanol), m. p. 210—210·5° after further crystallisation from ether (Found: C, 73·9; H, 7·55; N, 2·7. $C_{31}H_{37}O_5N$ requires C, 73·9; H, 7·4; N, 2·8%). Concentration of the mother-liquor and dilution with ether gave a second crop of slightly crude material (0·24 g.).

(+)- *and* (−)-α-3-*Hydroxygrisan*-4′-*yl* (−)-N-*Menthylphthalamate*.—Preliminary experiments indicated that the quality and yield of the product of this reduction depended rather critically on the conditions. The best results were obtained as follows: α-3-Oxogrisan-4′-yl (−)-*N*-menthylphthalamate (300 mg.) in methanol (10 ml.) at 0° was treated with sodium borohydride (25 mg.) with shaking. The mixture was then set aside overnight at 0°. Solutions from twelve such experiments were combined, diluted with 0·1N-hydrochloric acid, and extracted with ether, the extract being washed with water, dried, and evaporated to a gummy solid (3·52 g.) which was boiled with a little ether, cooled at 0°, and filtered. This gave a mixture of the diastereoisomeric α-3-hydroxygrisan-4′-yl (−)-*N*-menthylphthalamates (1·88 g.), m. p. 197—200°.

Six recrystallisations of this material from benzene yielded (−)-α-3-*hydroxygrisan*-4′-*yl* (−)-N-*menthylphthalamate* (0·49 g.), m. p. 218—219°, $[\alpha]_D$ − 57° (*c* 0·9 in ethanol) (Found: C, 73·8; H, 8·0; N, 2·6. $C_{31}H_{39}O_5N$ requires C, 73·6; H, 7·8; N, 2·8%). A further quantity (total 0·78 g.) of the same diastereoisomer was obtained during subsequent fractionation the progress of which was, however, difficult to follow at first because of the occasional separation of a solvated, sparingly soluble, voluminous crystalline solid, m. p. 136—141° (gas evolution) followed by resolidification and remelting at *ca.* 190—194°, $[\alpha]_D^{20}$ −24° (*c* 1·0 in ethanol) after drying at 80° for 45 min. Recrystallisation of such material from fresh solvent led to a first crop of unsolvated (−)-diastereoisomer of reasonably good quality.

As no solvent could be found to reverse the relative solubilities of the two diastereoisomers the fractionation was continued in benzene. Concentration of the mother-liquor five times, with removal of intermediate crops of solid mixtures, yielded a solution which showed a positive rotation. Evaporation yielded a gum (293 mg.) which crystallised from ether to yield needles (194 mg.) of (+)-α-3-*hydroxygrisan*-4′-*yl* (−)-N-*menthylphthalamate*, m. p. 185—186°, $[\alpha]_D^{21}$ +10° (*c* 1·1 in ethanol) or +19° (*c* 1·0 in benzene) (Found: C, 73·5; H, 8·1; N, 3·2%). On repeated crystallisation of this compound from ether its m. p. at first rose to 186·5—187·5°, then fell to 178—184°, and finally rose to 188—190° whilst the specific rotation remained virtually constant ($[\alpha]_D$ +10°, +11°, +10°, in ethanol).

The residue (1·65 g.) obtained by evaporation of the original mother-liquor was chromatographed on alumina (50 g.) in ether. Elution with ether (total 150 ml.) yielded a gum (437 mg.),

crystallisation of which from light petroleum (b. p. 40—60°)–ether gave prisms (314 mg.), m. p. 108—109°, of (−)-*N*-menthylphthalimide, identified by undepressed m. p. on admixture with authentic material. Subsequent fractions, eluted at first with ether but later with ether containing acetone (0·25%), yielded a solid (300 mg.), m. p. 146—175° raised to 160—178° on crystallisation from ether, $[\alpha]_D^{20}$ −5° (ethanol), identified as α-grisan-3 : 4′-diol by comparison of infrared spectra. Elution was completed by means of benzene–acetone (199 : 1, changing to 99 : 1) and yielded a gum (900 mg.) which, after dissolution in benzene and separation of an unidentified solid (277 mg.), m. p. 182—184°, $[\alpha]_D$ −12° (in benzene), showed a positive rotation, and was again chromatographed on alumina (50 g.) in benzene. Elution with benzene–acetone (95 : 5) yielded solid fractions (total 454 mg.), m. p. 180—185°, which were combined and crystallised from ether, affording (+)-α-3-hydroxygrisan-4′-yl (−)-*N*-menthylphthalamate (287 mg.), $[\alpha]_D$ +21° (in benzene), $[\alpha]_D$ +11° (in ethanol), m. p. 187·5—189° undepressed on admixture with the specimen obtained previously.

(+)-α-*Grisan*-3 : 4′-*diol*.—(+)-α-3-Hydroxygrisan-4′-yl (−)-*N*-menthylphthalamate (170 mg.) was heated under reflux for 1 hr. with 2N-potassium hydroxide (2 ml.). After cooling, the mixture, in which oily crystals were suspended, was diluted with a little water which dissolved the oil, cooled at 0°, and filtered, yielding leaflets (50 mg.) of (+)-α-*grisan*-3 : 4′-*diol*, m. p. 203—205°, $[\alpha]_D^{21}$ +73° (*c* 1·0 in ethanol) (Found: C, 71·15; H, 7·2. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). After recrystallisation from benzene–acetone the product, of unchanged rotation, melted gradually between 170° and 202°. The infrared spectrum was identical with that of (±)-α-grisan-3 : 4′-diol (above), the (−)-α-diol (below), and material isolated from the shoots of plants of the broad bean which had been grown on an aqueous solution of grisan-3 : 4′-dione.[1]

(−)-α-*Grisan*-3 : 4′-*diol*.—Hydrolysis of (−)-α-3-hydroxygrisan-4′-yl (−)-*N*-menthylphthalamate under the same conditions afforded leaflets of (−)-α-*grisan*-3 : 4′-*diol*, $[\alpha]_D^{20}$ −73° (*c* 0·8 in ethanol), m. p. 206—207° from benzene–acetone (Found: C, 70·55; H, 7·3%). Further crystallisation from benzene caused a depression in m. p., affording needles which softened *ca.* 190°, melting mainly 192—198°.

(±)-β-*Grisan*-3 : 4′-*diol*.—β-4′-Hydroxygrisan-3-*one* (253 mg.) in methanol (0·5 ml.) and water (0·2 ml.) at 8° was treated with sodium borohydride (35 mg.). The mixture, in which crystals of ketol had separated, was gently shaken and became homogeneous after 5 min. Almost immediately crystals separated. After being kept overnight at 4° these were filtered off and washed with cold water, yielding leaflets (235 mg.) of (±)-β-*grisan*-3 : 4′-*diol*, m. p. 171—175°, softening 169° (Found: C, 70·9; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%), $\lambda_{max.}$ (in ethanol) 281, 287·5 mμ (log ε 3·51, 3·46). Recrystallisation yielded clusters of prisms, m. p. 131—139°, from benzene, or prisms, m. p. 168—176°, softening at 156°, from methanol–water (1 : 2).

The author is indebted to Dr. L. A. Duncanson for the measurement and interpretation of the infrared spectra, and to Messrs. D. C. Aldridge, A. P. Green, and A. Morrison for experimental assistance.

AKERS RESEARCH LABORATORIES, IMPERIAL CHEMICAL INDUSTRIES LIMITED,
THE FRYTHE, WELWYN, HERTS. [*Received, September 4th*, 1958.]

XUM

955. *The Catalytic Hydrogenation of Unsaturated Hydrocarbons. Part III.* The Kinetics of the Hydrogenation of Acetylene over Various Types of Nickel Catalyst.*

By G. C. Bond and R. S. Mann.

An expression of the form $-dp/dt = k_A P_{H_2} + k_B(P_{H_2} - P_{H_2}^{\circ})$ describes the rate-dependence on hydrogen pressure over nickel–kieselguhr, regardless of the order of admission of the reactants to the reaction vessel. Results with three nickel powders also conform to this expression when hydrogen is admitted first; they are poisoned if acetylene is added first. Rates are generally independent of acetylene pressure. The results presented in Part I have been broadly confirmed: E_B lies between 15 and 29 kcal./mole, and E_A between 6 and 13 kcal./mole. The mean ratio E_B/E_A is 2·4 for supported catalysts and is somewhat lower for the powders.

In disagreement with earlier findings, $P_{H_2}^{\circ}$ has been found to be either independent of, or to increase only slightly with, increasing acetylene pressure; it normally decreases with increasing temperature. Possible reasons for the disagreement are discussed. Nickel–kieselguhr shows the highest activity, and of the powders that prepared by reduction of the oxide *in situ* is most efficient.

Hydrogenation of acetylene has been little studied on nickel catalysts other than those of the pumice-supported type.[1,2] Evaporated nickel films [3] and nickel wires [4] are both substantially poisoned by acetylene and are therefore not suitable forms to use. de Pauw and Jungers [5] reported that nickel–kieselguhr failed to catalyse the reaction when acetylene was admitted first to the reaction vessel, but gave exceedingly fast rates when hydrogen was admitted first. We have failed to confirm these observations. With nickel powder, obtained by reduction of the nitrate, they failed to find constant activity even when hydrogen was admitted first, but they secured reproducible activity by reducing the powder between each run; our work has not confirmed the necessity for this.

In Part I [1] a complex rate expression was proposed to account for the results obtained over a nickel–pumice catalyst when the initial hydrogen : acetylene ratio was greater than about two. We now confirm this and extend the observations to examine whether this form of rate expression is shown by other types of nickel catalyst.

Experimental

Apparatus, purification, and procedure were essentially as described in Part I,[1] except that the catalyst invariably lay at the bottom of the reaction vessel. In later experiments the vessel was slightly modified to permit the reduction of the catalyst in a hydrogen steam.

Catalysts.—Nickel–pumice (containing about 10% of metal by weight) was prepared as before.[1] Nickel–kieselguhr was obtained unreduced from the British Petroleum Company; it was reduced in a slow stream of hydrogen at 450° for 12 hr. and contained 10% of metal by weight. Nickel powder prepared by the decomposition of nickel carbonyl was provided by the Mond Nickel Company. Two other types of nickel powder were prepared: (i) " AnalaR " nickel nitrate was calcined in a stream of oxygen at 250° for 8 hr. and the resulting oxide reduced in a stream of hydrogen at 300° for 10 hr. (ii) Basic nickel carbonate, precipitated from nickel nitrate solution by ammonium hydrogen carbonate, was dried at 105° and sintered at 400°. A portion of the resulting oxide was reduced in a slow stream of hydrogen in the reaction vessel at 500° for 24 hr.[6]

* Part II, *J.*, 1958, 4288.

[1] Bond, *J.*, 1958, 2705.
[2] Sheridan, *J.*, 1944, 373; 1945, 133.
[3] Beeck, *Discuss. Faraday Soc.*, 1950, **8**, 118; Wheeler, personal communication.
[4] Farkas, Farkas, and Rideal, *Proc. Roy. Soc.*, 1934, *A*, **146**, 630.
[5] de Pauw and Jungers, *Bull. Soc. Chim. belges*, 1948, **57**, 618.
[6] Best and Russell, *J. Amer. Chem. Soc.*, 1954, **76**, 838.

Samples not initially reduced in the reaction vessel were treated with hydrogen (*ca.* 100 mm.) *in situ* at 300° for ½ hr. before use. The surface areas of the Mond Nickel powder and that prepared by method (ii) were determined after use by krypton adsorption at −196°.

Results

Nickel–Pumice Catalysts.—Experiments were carried out on samples drawn from two preparations; batch I, from which the samples used in Part I were drawn, gave samples B (0·51 g.) and B* (1·00 g.; identical with B of Part I), and batch II, a fresh preparation, gave samples D (0·21 g.), E (0·50 g.), and F (0·50 g.). Preliminary observations on B differed from some of those in Part I: thus for example while a rate expression of the form

$$-(\mathrm{d}p/\mathrm{d}t)_0 = k_A P_{H_2} + k_B(P_{H_2} - P_{H_2}^\circ) \quad . \quad . \quad . \quad . \quad (1)$$

was still found when acetylene was admitted before hydrogen, pressure–time curves with initial hydrogen pressures greater than $P_{H_2}^\circ$ were not invariably of the linear (Type I) form. Instead they showed two linear parts (a Type IIA curve) with the point of intersection, $-\Delta P_\alpha$, increasing from about $2/3P_{C_2H_2}$ to $P_{C_2H_2}$ (where $P_{C_2H_2}$ is the initial acetylene pressure) with increasing initial hydrogen : acetylene ratio between 2 and 6 at 100°. Type III curves were still, however, obtained below $P_{H_2}^\circ$. In addition, the sample from batch I no longer showed the previously-found proportionality between $P_{H_2}^\circ$ and $P_{C_2H_2}$, and instead the former was broadly independent of the latter. For these reasons a second batch of catalyst was prepared but samples from this batch also showed behaviour not conforming with earlier work.

Since in all cases type IIA curves were found with initial hydrogen pressures greater than $P_{H_2}^\circ$, the general rate expressions are

$$-\mathrm{d}p/\mathrm{d}t = k_A P_{H_2} + k_\alpha(P_{H_2} - P_{H_2}^\circ) \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and
$$-\mathrm{d}p/\mathrm{d}t = k_A P_{H_2} + k_\beta(P_{H_2} - P_{H_2}^\circ) \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $k_A + k_\alpha$ is the slope of the line obtained on plotting R_α against initial hydrogen pressure, and $k_A + k_\beta$ is the slope obtained when R_β is so plotted. The results will therefore be described in terms of the temperature- and acetylene pressure-dependence of the first-order rate constants k_A, k_α, and k_β and of $P_{H_2}^\circ$. Table 1 shows the activation energies, E_i, and the logarithms

Table 1. *Activation energies (kcal./mole) and pre-exponential factors for nickel–pumice.*

Sample	B	B*	Part I	D	E	F
Temp. range	100—115°	53—83°	86—110°	115—160°	85—130°	111—135°
E_A	9·6	10·5	10·3	9·2	8·2	6·4
E_α	24·2	21·2	23·8	22·0	18·2	16·0
E_β	—	—	—	22·8	19·0	—
ΔE_α	15·0	10·5	13·5	12·8	10·5	10·1
ΔE_β	—	—	—	14·6	12·3	—
$\log_{10} A_A$	4·0	5·2	5·3	3·3	2·9	2·1
$\log_{10} A_\alpha$	12·2	12·1	12·5	10·3	8·7	7·3
$\log_{10} A_\beta$	—	—	—	9·5	10·7	—
$\log_{10} \Delta A_\alpha$	8·7	6·7	7·8	6·9	6·0	5·4
$\log_{10} \Delta A_\beta$	—	—	—	8·6	6·8	—

of the pre-exponential factors, A_i [expressed as min.$^{-1}$ (g. of metal)$^{-1}$], obtained from the corresponding k_i's by the Arrhenius equation, while other quantities are related as

$$\log_{10}(k_\alpha/k_A) = \log_{10}\Delta A_\alpha - \Delta E_\alpha/2{\cdot}3\,RT; \quad \log_{10}(k_\beta/k_A) = \log_{10}\Delta A_\beta - \Delta E_\beta/2{\cdot}3RT$$

The initial acetylene pressure was 30 mm. in all series where it was not purposely varied. The sample B* gave type I curves above $P_{H_2}^\circ$ and values for E_β, etc., are not therefore quoted in the table. Values of E_β etc., for samples B and F are too inaccurate to quote. Mean values and standard deviations for E_A, E_α, and E_α/E_A are respectively 9·0 ± 1·2 (±13%), 20·9 ± 2·5 (±12%), and 2·34 ± 0·15 (±6·5%); the quotient E_α/E_A is thus much less variable than either activation energy separately. A convincing " compensation effect " of the form $\log_{10} A_i = 0{\cdot}55\,E_i$ holds for all samples except B*.

XUM

With samples B and B*, $P_{H_2}°$ was roughly independent of temperature, the mean values being respectively 62 and 98 mm.; for sample D it was 75, 69, 66, and 65 mm. at 115°, 130°, 145°, and 160°; for E it was 80, 74, 63, and 57 mm. at 85°, 100°, 115°, and 130°, respectively. In all cases the initial acetylene pressure was 30 mm.

For sample F the behaviour was irregular; when the dependence of the parameters on initial acetylene pressure, $P_{C_2H_2}$, was studied over it the results were complicated by a continuously increasing activity. At 120° and 135°, however, $P_{H_2}°$ was approximately independent of $P_{C_2H_2}$ between 15 and 90 mm., the mean value for eight series of experiments being 83 ± 10 mm. The quotient k_α/k_A was independent of $P_{C_2H_2}$ at each temperature.

Over sample F between 90° and 120°, type IIA curves were obtained when hydrogen was admitted before the acetylene, whereas type IIB curves were previously [1] obtained under these conditions; however the same rate expressions still describe the results. The ratio k_α/k_β was independent of temperature and the mean value, 1·20, agrees well with those quoted in Table 4 of Part I (1·15—1·22). The activation energies E_α and E_β (not determined previously since the activities were not comparable) are respectively 14·5 and 14·1 kcal./mole, much larger than the value of E_α (6·4 kcal./mole) found when the reverse order of addition was employed.

Nickel–Kieselguhr Catalyst.—Four samples of the nickel–kieselguhr catalyst had the following weights: A, 0·29 g.; B, 0·10 g.; C, 0·12 g.; D, 0·14 g. The rate expressions (2) and (3) applied under all conditions, acetylene being admitted before the hydrogen; pressure–time curves were invariably of type IIA above $P_{H_2}°$ and of type III below it. $-\Delta p_\alpha$ was essentially independent of both initial hydrogen pressure and temperature. The temperature-dependence of the first-order rate constants is given in Table 2, the fixed initial acetylene pressure being 30 mm.;

TABLE 2. *Activation energies (kcal./mole) and pre-exponential factors for nickel–kieselguhr.*

Sample	E_A	E_α	ΔE_α	$\log_{10} A_A$	$\log_{10} A_\alpha$	$\log_{10} \Delta A_\alpha$
A	12·8	27·4	17·3	6·8	16·4	10·4
B	12·1	28·8	16·9	6·3	16·3	10·0
D	9·2	25·6	18·7	4·7	15·2	11·3
Mean	11·4 ± 1·4	27·3 ± 1·1	17·6 ± 0·7	—	—	—

sample C was used at only one temperature. Variations of k_β with temperature followed closely those of the k_α, so no values for E_β, etc., are quoted. The " compensation effect " is described by the equation $\log_{10} A_i = 1·0 + 0·65 E_i$, and the mean value of E_α/E_A is 2·40 ± 0·27.

Values of k_A and k_α were independent of the fixed initial acetylene pressure used. For example, in series of experiments carried out over sample D at 60° with fixed initial acetylene pressures of 15, 30, 60, and 90 mm., the resulting mean values of k_A and k_α were respectively $(3·45 \pm 0·25) \times 10^{-2}$ min.$^{-1}$ and $(8·92 \pm 0·09) \times 10^{-2}$ min.$^{-1}$. That the reaction is strictly of zero order in acetylene was confirmed by series of initial-rate measurements made at 60° and 80° with a fixed initial hydrogen pressure of 60 mm. and acetylene pressures varying between 10 and 120 mm. Rates were always independent of the variable pressure provided $P_{H_2}/P_{C_2H_2}$ exceeded 0·5. The various samples of this catalyst behaved much more consistently than did those of nickel–pumice. For example, the mean values of the acetylene pressure-independent quotient k_α/k_A at 60° were respectively 1·12, 1·00, 1·09, and 1·07 for the four samples.

The dependence of $P_{H_2}°$ on acetylene pressure is described by the equation (4). Values of

$$\log_{10} (P_{H_2}°/P_{C_2H_2}) = \log_{10} k - x \log P_{C_2H_2} \quad . \quad . \quad . \quad . \quad . \quad (4)$$

log k and x (within error the same for all samples and dependent only on temperature) were respectively 1·58 and 0·73 at 60°, 1·45 and 0·69 at 70°, and 1·31 and 0·65 at 80°.

One series of experiments was performed over sample D at 80°, hydrogen being admitted first; type IIA curves were obtained at all hydrogen pressures, and the rate expression (2) was valid. Its parameters had the values: $P_{H_2}°$, 50 mm.; k_A, $9·2 \times 10^{-2}$ min.$^{-1}$; k_α, $42·0 \times 10^{-2}$ min.$^{-1}$. Reversal of the order of addition therefore reduces $P_{H_2}°$ (71 to 50 mm.) and approximately doubles both k_A and k_α, leaving their ratio unaffected.

Nickel Powder Catalysts.—The characteristics of the samples were as follows: Samples A (0·220 g.) and B (0·215 g.) were produced by reduction of the oxide from the nitrate, C (0·240 g.)

was produced by reduction of the oxide from the basic carbonate and had a surface area of 0·41 m.²/g., and D (0·165 g.) was from the Mond Nickel Co. and had a surface area of 1·48 m.²/g. Prior addition of acetylene to sample A at 150° led to rapid poisoning, which however was counteracted by a short reduction at 300°. In all subsequent experiments with the powders, hydrogen was admitted before acetylene, and no poisoning then occurred. Type III curves were always obtained with hydrogen pressures less than $P_{H_2}°$; at higher pressures, type IIA curves were obtained with samples A and B, and type I curves with C and D.

Activation energies and pre-exponential factors obtained from series of experiments in which the initial acetylene pressure was 30 mm. are given in Table 3; the subscript (α, B) indicates that the quoted activation energies, etc., are values of E_α for samples A and B [where the rate expressions (2) and (3) hold], and are values of E_B for C and D [where the appropriate rate expression is equation (1)]. No values are quoted for E_β, etc., since the variations of k_β with temperature were not sufficiently regular. The "compensation effect" equation is $\log_{10} A_i = 0{\cdot}40 + 0{\cdot}48E_i$.

TABLE 3. *Activation energies (kcal./mole) and pre-exponential factors for nickel powders.*

Sample ...	Temp. range	E_A (kcal./mole)	$E_{(\alpha, B)}$ (kcal./mole)	$\Delta E_{(\alpha, B)}$ (kcal./mole)	$\log_{10} A_A$	$\log_{10} A_{(\alpha, B)}$	$\log_{10} \Delta A_{(\alpha, B)}$
A	107—150°	11·4	18·3	8·6	5·5	9·2	4·7
B	124—150°	6·4	16·0	9·1	3·0	8·2	5·2
C	73—150°	8·2	15·1	7·3	5·0	8·3	4·4
D	88—126°	9·2	15·6	5·5	4·8	8·0	3·0

The effect of variation in acetylene pressure was examined only with sample B, on which experiments at 124°, 140°, and 150° with fixed initial acetylene pressures of 15, 30, 60, and 90 mm. showed that k_A and k_α were both independent of it. At the same temperatures, and with a fixed initial hydrogen pressure (60 mm.), initial rates were accurately independent of acetylene pressure within the range 10—120 mm. Samples A and B gave reasonably consistent values of k_α/k_A: values at 124°, 140°, and 150° were respectively 0·85 and 0·87; 1·42 and 1·24; and 1·88 and 1·79. Equation (4) again describes the dependence of $P_{H_2}°$ on $P_{C_2H_2}°$; over sample B, x was 0·75 (independent of temperature) while at 124°, 140°, and 150° the values of log k were respectively 1·64, 1·58, and 1·50. Over sample A, $P_{H_2}°$ declined smoothly with increasing temperature (107—150°) from 90 to 50 mm., and a similar decline from 170 to 125 mm. was observed with sample D in the range 90—126°. The last values are abnormally high. With sample C, $P_{H_2}°$ was not dependent on temperature (73—114°) and had a mean value of 101 ± 10 mm.

DISCUSSION

This more extensive study of the kinetics of hydrogenation of acetylene over nickel catalysts has revealed a very complex pattern of results. There is no apparent consistency between the types of pressure–time curve found for supported nickel catalysts and the experimental conditions. Whereas previously [1] type I curves resulted on prior admission of acetylene to nickel–pumice, type IIA curves are now found with samples drawn from the same and from a new batch: the age of the catalyst is not therefore the sole variable. On re-examining a previously used sample (B*), the previous behaviour was found. Following prior admission of hydrogen to nickel–pumice, curves of type I,[2] type IIB,[1] and type IIA (present work) have been found. The observations may be summarised as follows. (i) Reasonably fresh nickel–pumice may yield, on prior admission of acetylene, curves of either type I or IIA, and on prior admission of hydrogen one of three types: the precise conditions of preparation and reduction may be decisive. (ii) On prolonged storage, nickel–pumice will yield type IIA curves (whereas type I curves were originally given), unless the sample had been used soon after its preparation.

However, it is possible for initial rates determined from different types of pressure–time curve to conform to similar rate expressions. Thus, nickel–pumice being used, a rate expression of the form of equation 1 is obtained regardless of whether the curves are of

type I [1] or IIA (present work), provided only acetylene is admitted first, while the equation

$$-(\mathrm{d}p/\mathrm{d}t)_0 = k_{\alpha'}P_{H_2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

holds over a wide range of conditions when hydrogen is added first, regardless of the form of the pressure–time curve form (refs. 1 and 2 and this work). It is therefore concluded that the form of the rate expression is more fundamental than the form of the pressure–time curves. Possible effects of the order of addition on the mechanism were discussed in Part I, and that differing mechanisms do operate (depending on the addition order) is confirmed by the finding that for nickel–pumice (sample F) E_A is 6·4 kcal./mole while $E_{\alpha'}$ is 14·5 kcal./mole. The α- and the β-part of the type IIA curves found in this work are not kinetically independent, for the activation energies E_α and E_β (where the latter could be accurately estimated) are not significantly different.

Nickel–kieselguhr and the powders differ from nickel–pumice in that they show the complex rate expression even when hydrogen is admitted first. Mean values of E_A and especially of E_α vary considerably between the various catalyst types, but it is perhaps significant that the mean values of E_α/E_A are practically identical for the two supported catalysts (2·34 and 2·40); this ratio is somewhat lower (*ca.* 1·9) for the powders.

It is evident from the differing temperature ranges in which the various samples were studied that there exist substantial differences in activity per unit weight of metal. Because of the " compensation effect," activities at an arbitrary temperature are a better guide than pre-exponential factors, and Table 4 gives the approximate mean values of

TABLE 4. *Approximate mean values of rate constants* (*min.*$^{-1}$ *g.*$^{-1}$) k_A *and* $k_{(\alpha, B)}$ *at* 100°.

Sample	Ni–pumice	Ni–kieselguhr	Powders A & B	Powder C	Powder D
10^2k_A	47	600	1·0	24	9·0
$10^2k_{(\alpha, B)}$	21	7700	4·0	28	9·5

k_A and $k_{(\alpha, B)}$ at 100° (results for sample B* of nickel–pumice are not included). Since the relative activities will vary with temperature, it is not the precise values, but only their orders of magnitude, which are significant. Nickel–kieselguhr is much more active than nickel–pumice, which may be due to a large difference in crystallite size. Amongst the powders, C is by far the most active, and this may be because it was never exposed to air after reduction. The batch from which samples A and B were taken may have been slightly pyrophoric after reduction, and so have been sintered when first exposed to air, with consequent loss of area and subsequent activity. The *specific* activities of samples C and D are more disparate than the activities quoted above, the specific rate constants for C being both about ten times greater than for D. The specific area of C (0·41 m.^{2}/g.), determined after use, may be much less than when in use, again because of sintering on exposure to air. The high activity of nickel–kieselguhr is accompanied by consistently high activation energies. The ready poisoning of unsupported nickel by acetylene has been confirmed.

$P_{H_2}^\circ$ generally decreases with increasing temperature. In Part II it was suggested that the second mechanism (whose rate constants are k_B or k_α and k_β) was initiated by molecularly adsorbed hydrogen. $P_{H_2}^\circ$ was previously [1] found to be proportional to $P_{C_2H_2}$, and a possible mechanism invoking competition between physically adsorbed acetylene and molecularly adsorbed hydrogen for the surface above the primary chemisorbed layer was discussed. This behaviour has however not been repeated, and $P_{H_2}^\circ$ now appears to be either approximately independent of $P_{C_2H_2}$ (nickel–pumice F and powder C) or proportional to about $(P_{C_2H_2})^{0\cdot3}$ (nickel–kieselguhr and powders A, B, and D). A possible interpretation is that here incremental acetylene pressures are respectively ineffective and only weakly (and progressively less) effective in inhibiting molecular hydrogen adsorption. $P_{H_2}^\circ$ decreases with rising temperature, except, significantly, in those cases where it is

also broadly independent of acetylene pressure. In the other cases, the explanation may be that with rising temperature the physically adsorbed acetylene is desorbed, thus reducing the minimum hydrogen pressure required to give molecular adsorption.

We thank the British Petroleum Co. Ltd. and the Mond Nickel Co. Ltd. for gifts of nickel catalysts, Mr. D. A. Dowden of Imperial Chemical Industries Limited (Billingham Division) for the determination of the surface areas, and the University of Hull for a Maintenance Grant (to R. S. M.).

THE UNIVERSITY, HULL. [*Received, August 12th,* 1958.]

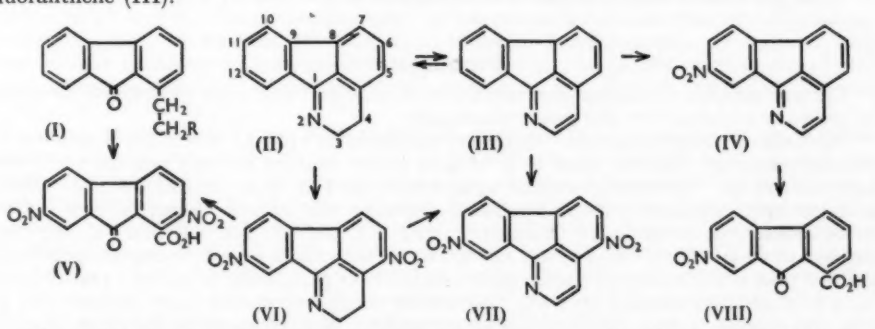
---

956. *The Synthesis and Properties of 2-Azafluoranthene.*

By NEIL CAMPBELL and KENNETH F. REID.

The syntheses of 3 : 4-dihydro-2-azafluoranthene and 2-azafluoranthene are described. The latter substance is reduced to the former by sodium amalgam and ethanol and on nitration yields 12-nitro- and 5 : 12-dinitro-2-azafluoranthene.

2-AZAFLUORANTHENE (III) has been isolated from coal tar.[1] We have synthesised it by applying the Curtius reaction to β-(9-oxo-1-fluorenyl)propionic acid (I; R = CO_2H) to give the substituted ethylamine (I; R = NH_2), which with alkali affords 3 : 4-dihydro-2-azafluoranthene (II). This on dehydrogenation with palladised charcoal yields 2-azafluoranthene (III).



The amide (I; R = $CO{\cdot}NH_2$) undergoes the Hofmann reaction to yield directly impure dihydro-2-azafluoranthene (II), identified as the hydrochloride, methiodide, and picrate.

Nitration of 2-azafluoranthene yields 12-nitro- (IV) and 5 : 12-dinitro-2-azafluoranthene (VII). The constitution of the mononitro-compound follows from oxidation of its methiodide to 7-nitrofluorenone-1-carboxylic acid (VIII). The dinitroazafluoranthene was orientated by its preparation by the dehydrogenation of 3 : 4-dihydro-5 : 12-dinitro-2-azafluoranthene (VI) (obtained by nitration of 3 : 4-dihydro-2-azafluoranthene), whose constitution is established by its oxidation to 2 : 7-dinitrofluorenone-1-carboxylic acid [2] (V). The structure of this acid was established by decarboxylation to 2 : 7-dinitrofluorenone.[3] The formation of 12-nitro-2-azafluoranthene is not unexpected since 4-azafluoranthene also undergoes nitration at position 12.[4]

Reduction of 2-azafluoranthene with 5% sodium amalgam and ethanol yields 3 : 4-dihydro-2-azafluoranthene, a somewhat surprising result since 3 : 4-dihydro-products

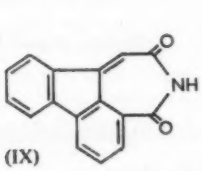
[1] Kruber, *Chem. Ber.*, 1949, **82**, 199; Oberkobusch, *ibid.*, 1953, **86**, 975.
[2] Garascia, Fries, and Ching, *J. Org. Chem.*, 1952, **17**, 226.
[3] Campbell and Stafford, *J.*, 1952, 299; A. Temple, Thesis, Edinburgh, 1954.
[4] Koelsch and Steinhauer, *J. Org. Chem.*, 1953, **18**, 1516; Campbell and Keir, *J.*, 1955, 1233.

XUM

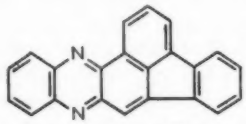
arising from the reduction of fluoranthene, quinoline, or *iso*quinoline have not been reported.[5] Reduction of 2-azafluoranthene or its dihydro-derivative with tin and hydrochloric acid yields 1 : 2 : 3 : 4-tetrahydro-2-azafluoranthene.

The absorption spectrum of 2-azafluoranthene contains three groups of bands and closely resembles that of fluoranthene.[6]

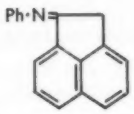
It was hoped that fluoranthene-3 : 4-quinone would react with hydrazoic acid to give



(IX)



(X)



(XI)

3-hydroxy-4-aza- or 4-hydroxy-3-aza-fluoranthene,[7] but the product was the imide (IX), whose structure was proved by hydrolytic degradation to fluorene-1-carboxylic acid. 1-Carboxylfluorenylideneacrylic acid is presumably an intermediate since fluorenylideneacrylic acid undergoes alkaline hydrolysis to fluorene. Our results emphasise the highly specific nature of the reaction of hydrazoic acid with *o*-quinones, since 1 : 2-naphthaquinone yields 4-amino-1 : 2-naphthaquinone, phenanthraquinone affords phenanthridone, and acenaphthenequinone yields naphthalic anhydride (probably *via* the imide).[8] Fluoranthenequinone reacts with *o*-phenylenediamine, giving 9 : 14-diazanaphtho[2 : 3-*b*]-fluoranthene (X).

Acenaphthenone with hydrazoic acid in benzene gives the anil (XI).

Experimental

Chromatographic separations were effected on alumina, and ultraviolet spectra were measured by means of a Unicam SP. 500 spectrophotometer.

Synthesis of 2-Azafluoranthene.—Activated sodium azide[9] (2·6 g.) was added to β-(9-oxo-1-fluorenyl)propionyl chloride (from 10 g. of acid) in dry benzene (50 ml.) and the whole was heated for 20 hr. The filtered solution, when heated for 4 hr. with concentrated hydrochloric acid (50 ml.), deposited β-(9-*oxo*-1-*fluorenyl*)*ethylamine hydrochloride*, greenish-yellow plates (from dioxan), m. p. 210—211° (Found: C, 69·2; H, 5·4; N, 5·5; Cl, 13·6. $C_{15}H_{14}ONCl$ requires C, 69·4; H, 5·4; N, 5·4; Cl, 13·7%), which with alkali gave 3 : 4-dihydro-2-azafluoranthene [*hydrochloride*, orange needles (from ethanol–light petroleum), m. p. 193—194° (Found: N, 5·5. $C_{15}H_{13}NCl$ requires N, 5·8%; *methiodide*, orange-red needles (from ethanol), m. p. 252—253 (Found: I, 36·2. $C_{16}H_{14}NI$ requires I, 36·6%); *picrate*, orange needles (from ethanol), m. p. 229—230° (decomp.) (Found: N, 12·6. $C_{21}H_{14}O_7N_4$ requires N, 12·9%)]. The dihydroazafluoranthene was obtained in 40% yield by the action of sodium hypobromite on β-(9-*oxo*-1-*fluorenyl*)*propionamide*, yellow needles (from aqueous ethanol), m. p. 193—194° (Found: C, 76·5; H, 5·4; N, 5·4. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%).

5% Sodium amalgam (40 g.) was added in small portions to 2-azafluoranthene (2 g.) in boiling ethanol (80 ml.), the solution boiled for 2 hr., the volume reduced to 50 ml., and the residue neutralised with concentrated hydrochloric acid and poured into water (400 ml.). The suspension was extracted with ether, and the extract dried (Na_2SO_4) and evaporated. The residual oil was chromatographed with light petroleum as solvent and developer. Elution yielded first 3 : 4-dihydro-2-azafluoranthene (1·14 g.), characterised as the picrate and methiodide, and then starting material (0·28 g.).

[5] Knowles and Watt, *J. Amer. Chem. Soc.*, 1943, **65**, 410; Bohlmann, *Chem. Ber.*, 1952, **85**, 390; Jackman and Packham, *Chem. and Ind.*, 1955, 360.

[6] Orchin and Woolfolk, *J. Amer. Chem. Soc.*, 1946, **68**, 1727; Clar, Stubbs, and Tucker, *Nature*, 1950, **166**, 1075.

[7] Cf. Badger and Seidler, *J.*, 1954, 2329.

[8] Wolff, "Organic Reactions," John Wiley and Son, Inc., New York, 1947, Vol. III, p. 320; Stephenson, *J.*, 1949, 2620; Edwards and Petrow, *J.*, 1948, 1713.

[9] Nelles, *Ber.*, 1932, **65**, 1345.

2-Azafluoranthene.—Dihydroazafluoranthene (0·3 g.) was boiled for 3 hr. in 1-methylnaphthalene (5 ml.) with 20% palladised charcoal (0·05 g.) in an atmosphere of carbon dioxide. The mixture was filtered and the catalyst washed with benzene. The combined filtrate and washings were extracted with concentrated hydrochloric acid, and the acid layer was made alkaline. The precipitate, dissolved in ether, was washed with water and dried (Na_2SO_4). Evaporation of the ether yielded 2-azafluoranthene (0·285 g.), pale yellow needles, m. p. 91—92° (lit., 83°, 91—92°), $\lambda_{max.}$ 233, 254, 258, 280, 287, 308, 349, 355, and 365 mμ (log ε 4·4, 3·93, 3·95, 4·05, 4·0, 3·05, 3·70, 3·75, 3·80 respectively), $\lambda_{min.}$ 219, 250, 256, 262, 282, 306, 310, 350, 359 mμ (log ε 4·05, 3·87, 3·9, 3·9, 4·0, 3·03, 2·97, 3·69, 3·65) in *cyclo*hexane. This compound formed a *methiodide*, orange needles (from ethanol), m. p. 273° (decomp.) (Found: N, 4·0; I, 36·6. $C_{16}H_{12}NI$ requires N, 4·1; I, 36·8%), *trinitrobenzene complex*, pale yellow needles (from ethanol), m. p. 126—127° (Found: N, 12·8. $C_{21}H_{12}O_6N_4$ requires N, 13·5%), and *hydrochloride*, yellow needles, m. p. 208—209° (from ethanol–light petroleum) (Found: N, 5·6; Cl, 12·5. $C_{15}H_{10}NCl$ requires N, 5·9; Cl, 14·8%). The picrate is recorded [1] as having m. p. 222° but we found m. p. 239°.

2-Azafluoranthene (0·5 g.) or 3 : 4-dihydro-2-azafluoranthene hydrochloride (0·5 g.) was boiled with concentrated hydrochloric acid (20 ml.) and tin (10 g.) until the solution was nearly colourless. More acid (5 ml.) was added and the whole was heated until a colourless solution resulted. The cooled solution was decanted, made alkaline, and extracted several times with ether. The combined extracts were washed with water and dried (Na_2SO_4). Evaporation yielded 1 : 2 : 3 : 4-tetrahydro-2-azafluoranthene (0·2 g.), colourless needles (from light petroleum), m. p. 74—76°. It decomposed when dried and formed a *hydrochloride*, prisms (from light petroleum), m. p. 258—260° (decomp.) (Found: N, 5·6; Cl, 14·2. $C_{15}H_{14}NCl$ requires N, 5·8; Cl, 14·6%), and a *picrate*, yellow needles (from ethanol), m. p. 225—228° (decomp.) (Found: N, 12·8. $C_{21}H_{16}O_7N_4$ requires N, 12·8%).

5 : 12-Dinitro-2-azafluoranthene.—Dihydro-2-azafluoranthene (1 g.) was kept for 17 hr. in nitric acid (*d* 1·5; 8 ml.) at room temperature. It was poured into a stirred solution of potassium carbonate, and the resulting 3 : 4-*dihydro*-5 : 12-*dinitro*-2-*azafluoranthene* crystallised from toluene–light petroleum in brownish-yellow needles (0·7 g.), m. p. 278—284° (decomp.), the m. p. depending on the rate of heating (Found: C, 61·4; H, 2·9; N, 13·8. $C_{15}H_9O_4N_3$ requires C, 61·0; H, 3·1; N, 14·2%).

Chromic anhydride (1·2 g.) in acetic acid (5 ml.) and water (5 ml.) was added to the dihydrodinitro-2-azafluoranthene (0·9 g.) in boiling acetic acid (25 ml.) and the whole poured into water. The precipitate in benzene–chlorobenzene was chromatographed and development with this mixture gave 5 : 12-*dinitro*-2-*azafluoranthene*, yellow needles (from toluene–chlorobenzene), m. p. 300—301°, undepressed when admixed with the dinitro-2-azafluoranthene described below (Found: C, 61·2; H, 2·2; N, 14·0. $C_{15}H_7O_4N_3$ requires C, 61·4; H, 2·5; N, 14·3%). The same product was obtained by keeping 2-azafluoranthene (0·5 g.) for 20 hr. in nitric acid (*d* 1·5; 5 ml.) at room temperature or by nitration with concentrated nitric acid in acetic acid or potassium nitrate and concentrated sulphuric acid.

The dihydrodinitro-2-azafluoranthene (0·75 g.), 30% sulphuric acid (75 ml.), and potassium permanganate (2 g.) were boiled until the permanganate was decolorised. The mixture was then treated with sulphurous acid. The precipitate was extracted with chloroform, most of the solvent distilled off, and light petroleum added to precipitate 2 : 7-dinitrofluorenone-1-carboxylic acid, yellow needles (from chlorobenzene–light petroleum), m. p. and mixed m. p. 265—268°, yielding 2 : 7-dinitrofluorenone, m. p. 292°, when decarboxylated in quinoline at 180° in presence of a trace of copper.

12-Nitro-2-azafluoranthene.—2-Azafluoranthene and dilute acid gave the *nitrate*, yellow needles (from ethanol), m. p. 179° (Found: 67·8; H, 3·8; N, 11·2. $C_{15}H_{10}O_3N_2$ requires C, 67·7; H, 3·8; N, 10·5%). The nitrate (3·6 g.) was added slowly to concentrated sulphuric acid (18 ml.) with cooling and kept at room temperature for 1½ hr., then heated for 20 min. at 60° and poured into water. *12-Nitro-2-azafluoranthene* separated, and was boiled with potassium carbonate solution, dried, and crystallised from benzene in yellow needles (1·8 g.), m. p. 250—252° (Found: C, 71·7; H, 3·4; N, 11·0. $C_{15}H_8O_2N_2$ requires C, 72·6; H, 3·2; N, 11·3%). The nitro-compound (0·8 g.) was heated for 1 hr. in excess of methyl toluene-*p*-sulphonate at 100°. The mixture was extracted twice with hot benzene and once with ether. The metho-toluene-*p*-sulphonate, yellow needles (1 g.), m. p. 218—220°, was converted by precipitation with potassium iodide into the more readily crystallisable *methiodide* which separated from

aqueous ethanol in reddish-violet needles, m. p. 254—255° (Found: N, 7·1; I, 32·1. $C_{16}H_{11}O_2N_3I$ requires N, 7·2; I, 32·6%). Potassium permanganate (2 g.) in water (100 ml.) was added dropwise (4 hr.) to the methiodide (0·9 g.) in 10% potassium hydroxide solution (32 g.) at 60° and the solution having been kept at room temperature (1 hr.) was boiled and filtered. The manganese dioxide was extracted with boiling water, and the combined filtrates were acidified. The precipitate in chloroform was washed with water, dried (Na_2SO_4), evaporated to 1—2 ml. and when treated with light petroleum yielded 7-nitrofluorenone-1-carboxylic acid (0·05 g.), yellow needles (from acetic acid), m. p. and mixed m. p. 245—247°.

Fluoranthene-3 : 4-quinone.—The scant recorded description [10] of the preparation of the quinone requires supplementation. Chromic acid anhydride (15 g.) in water (10 ml.) and acetic acid (10 ml.) was added to fluoranthene (10 g.) in acetic acid (150 ml.) so that the temperature did not exceed 50°. The mixture was heated for 18 hr. on the water-bath, then poured into water (1·5 l.), and the brown-red precipitate was washed thoroughly with hot water. The precipitate in chloroform was extracted twice with 10% aqueous sodium carbonate, which on acidification gave fluorenone-1-carboxylic acid (4 g.), and the chloroform solution was reduced in volume and chromatographed. Development first with benzene and then benzene–chloroform (1 : 1 v/v) gave first fluoranthene (2 g.) and then the quinone (1·5 g.), red needles, m. p. 194° (lit., 188—189°), giving with *o*-phenylenediamine in acetic acid 9 : 14-*diazanaphtho*-[2 : 3-b]*fluoranthene*, yellow needles (from acetic acid), m. p. 229° (Found: C, 86·6; H, 3·8; N, 8·9. $C_{22}H_{12}N_2$ requires C, 86·8; H, 4·0; N, 9·2%).

Sodium azide (1·2 g., 0·018 mole) was added gradually to the quinone (1·4 g., 0·006 mole) in trichloroacetic acid (20 g.) at 60° with stirring, and heating was continued for 1 hr. Pouring into water (70 ml.) gave after several hours the *imide* (IX) (0·35 g.), subliming at 190—200°/0·1—0·5 mm. in yellow needles, m. p. 256° (Found: C, 77·5; H, 3·8; N, 6·1. $C_{16}H_9O_2N$ requires C, 77·7; H, 3·7; N, 5·7%). The imide (0·2 g.) was not hydrolysed by sulphuric or hydrochloric acid, but when boiled for 17 hr. with 20% sodium hydroxide solution (14 ml.) and acidified yielded fluorene-1-carboxylic acid (0·1 g.), m. p. and mixed m. p. 246—249°.

Fission of β-Fluorenylidenenacrylic acid.—Ethyl fluorenyl-9-glyoxylate, m. p. 85—87° (lit., 74—76°), α-hydroxy-9-fluorenylacetic acid, m. p. 205—206° (lit., 194—195°), and fluorenylideneacrylic acid, m. p. 228—229° (lit., 222—223°), were prepared by Wislicenus and Weitemeyer's method.[11] The acrylic acid (0·2 g.) was boiled for 6 hr. with sodium hydroxide (2·0 g.) in water (20 ml.). Fluorene (0·05 g.), m. p. and mixed m. p. 115°, collected in the condenser, and from the reaction mixture unchanged fluorenylideneacrylic acid (0·12 g.) was recovered.

Schmidt Reaction on Acenaphthenone.—Acenaphthenone yields a 2 : 4-*dinitrophenylhydrazone*, red needles (from xylene), m. p. 259—260° (Found: N, 15·9. $C_{18}H_{12}O_4N_4$ requires N, 16·1%). Hydrazoic acid (from 3·2 g. of sodium azide) in benzene was added to acenaphthenone (2·5 g.) in benzene (20 ml.) and concentrated sulphuric acid (4 ml.) and gave the *anil*, prisms (from ethanol), m. p. 93°, after chromatographic purification, blue fluorescence in solution (Found: C, 89·1; H, 5·6; N, 5·5. $C_{18}H_{13}N$ requires C, 88·9; H, 5·4; N, 5·8%).

Thanks are expressed to the British Petroleum Company, Ltd., for a grant.

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF EDINBURGH. [*Received, July 22nd*, 1958.]

[10] Goldschmiedt, *Ber.*, 1877, **10**, 2029.
[11] Wislicenus and Weitemeyer, *Annalen*, 1924, **436**, 1.

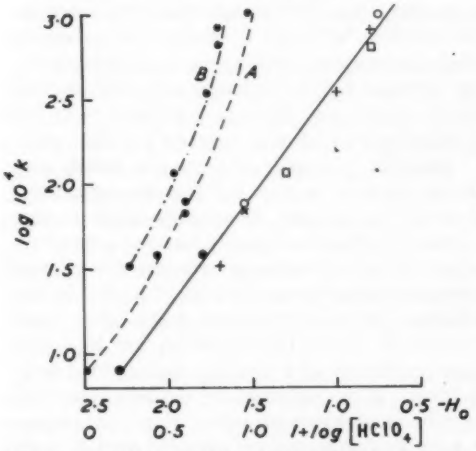
957. *Tracer Studies on Alcohols. Part IV.* The Oxygen Exchange and Racemisation of 4-Methoxydiphenylmethanol.*

By C. A. Bunton, D. R. Llewellyn, and I. Wilson.

The rates of oxygen exchange and racemisation of 4-methoxydiphenylmethanol in aqueous dioxan containing perchloric acid are very similar. The logarithms of the first-order rate constants are proportional to $-H_0$, with a slope of 1·2. The common slow step of these processes is therefore the heterolysis of the conjugate acid, ROH_2^+, of the alcohol. Because each single step of oxygen exchange gives complete racemisation, the life of the carbonium ion must be sufficiently long for it to become planar before it is captured by a water molecule.

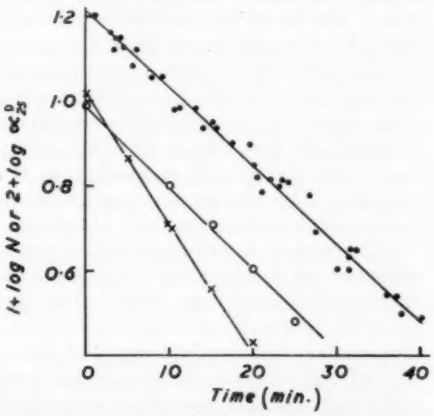
The stereochemical course of oxygen exchange between alcohols and water has been examined for two compounds, *viz.*, *sec.*-butyl alcohol[1] and 1-phenylethanol.[2] The asymmetric carbon atom of *sec.*-butyl alcohol is completely inverted at every exchange

Fig. 1. *Relation between rates and acidity.*



Dioxan–water (60 : 40 v/v): ○ Exchange, × racemisation.
Dioxan–water (40 : 60 v/v): + Exchange, □ racemisation.
● log k as a function of log $[HClO_4]$ in dioxan–water: *A* 60 : 40 v/v, *B* 40 : 60 v/v.

Fig. 2. *Racemisation and oxygen exchange.*



● Racemisation in dioxan–water (60 : 40 v/v); $[HClO_4] = 0·394$.
○ Exchange in dioxan–water (60 : 40 v/v); $[HClO_4] = 0·394$.
× Exchange in dioxan–water (40 : 60 v/v); $[HClO_4] = 0·350$.

of oxygen atoms, but for 1-phenylethanol this inversion is accompanied by considerable racemisation. This increase in racemisation, due to attachment of electron-releasing groups to the reaction centre, in a unimolecular substitution is well known.[3]

We have now investigated the acid-catalysed oxygen exchange between water and 4-methoxydiphenylmethanol, and the concurrent racemisation of the alcohol. The kinetics of exchange and racemisation were followed in aqueous dioxan containing perchloric acid, because the alcohol is only slightly soluble in water. The acidity function,

* Part III, *J.*, 1958, 403.

[1] Bunton, Konasiewicz, and Llewellyn, *J.*, 1955, 604; Bunton and Llewellyn, *J.*, 1957, 3402.
[2] Grunwald, Heller, and Klein, *J.*, 1957, 2604.
[3] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, Ltd., London, 1953, p. 387.

XUM

H_0, had been measured for perchloric acid in aqueous dioxan.[4] For a given composition of the medium the rates of exchange and racemisation agreed within experimental error (Fig. 1, Table 1), and the rate dependence was upon Hammett rather than stoicheiometric acidity, suggesting that the transition state does not contain a water molecule from the solvent.[5a, b]

TABLE 1. *Rates of oxygen exchange and racemisation in aqueous dioxan.*

Temp. 25°. *R* indicates racemisation.

	Dioxan–water (60 : 40 v/v)				Dioxan–water (40 : 60 v/v)			
$[HClO_4]_M$	0·101	0·265	0·394	0·936	0·182	0·350	0·530	0·630
H_0	*ca.* 2·3	1·8	1·55	0·75	*ca.* 1·7	1·3	1·0	0·80
10^4k (sec.$^{-1}$)...	0·8 0·82*R*	3·8 3·8*R*	7·5 7·0*R*	104	3·2*R*	12	35*R*	67 83*R*

DISCUSSION

Steric Course of Oxygen Exchange.—Complete racemisation with every substitution is the result expected for an S_N1 reaction which generates a long-lived carbonium ion.[3] The incoming reagent does not begin to form a covalent bond with the carbonium ion until the expelled group is sufficiently far away to exert no " shielding " effect. Nucleophilic attacks upon the carbonium ion from either the " front " or the " back " are then equally probable. In many of the systems studied, complete racemisation with substitution is not found for reactions with water or alcohols, although hydrolyses of carboxylic esters [6, 7a, b] provide examples of carbonium-ion intermediates which give racemic products.

The steric course of the oxygen exchange between 1-phenylethanol and water is very similar to that for the hydrolysis or alcoholysis of the optically active chloride.[2] It has been suggested that all these unimolecular substitutions have a common reaction path, in which the first step is formation of an " intimate " ion-pair of finite life, which may react with the solvent or reagent, or dissociate further to give a " solvent-separated " ion-pair. This in turn may react with the solvent, or reagent, or may dissociate further to give a free carbonium ion. Attack upon this will give a completely racemic product.

The original theory to explain the steric course of S_N1 reactions [3] envisaged a gradual extension of the breaking bond, with the reagent intervening from the " back " in the course of bond extension, rather than postulating a series of stable, or metastable, intermediates of structures between the initial reactant R–X and the carbonium ion R^+. Our observations on the steric course of the oxygen exchange of 4-methoxydiphenylmethanol do not differentiate between these possibilities; it is sufficient to suppose that the carbonium ion is completely free before the solvent molecule attacks. However, experiments on reactions of carboxylic esters of 4-methoxydiphenylmethanol [7a, b] and 2 : 4-dimethylhexan-4-ol [8] suggest that ion-pair intermediates are playing no essential part in the kinetics, or the steric course, of hydrolyses of these particular compounds in water or mixed aqueous–organic solvents.

Kinetic Form of Acid Catalysis.—A useful mechanistic test for acid-catalysed reactions is provided by the Zucker–Hammett hypothesis,[5a, 6] which suggested that the rate of acid-catalysed unimolecular hydrolysis, *A*-1, should be proportional to the acidity function $h_0 (= a_{H^+} . f_B/f_{HB^+}$, where B is a neutral base).

It is almost certain that oxygen exchange and racemisation of 4-methoxydiphenylmethanol is unimolecular. This system should give a correlation between rate constant and h_0. The logarithms of the rate constants for exchange and racemisation, in both solvents, are plotted against both the logarithm of $[HClO_4]$ and $-H_0$. The plots against concentration are curved and different for the two solvents, but against $-H_0$ they give

[4] Bunton, Ley, Rhind-Tutt, and Vernon, *J.*, 1957, 2327.
[5] (*a*) Zucker and Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2791; (*b*) Long and Paul, *Chem. Rev.*, 1957, **57**, 1, 935.
[6] Davies and Kenyon, *Quart. Rev.*, 1955, **9**, 203.
[7] (*a*) Bourns, Bunton, and Llewellyn, *Proc.*, 1957, 120; (*b*) Bunton and Hadwick, *J.*, 1957, 3043.
[8] Experiments quoted by Streitweiser, *Chem. Rev.*, 1956, **56**, 571.

the same straight line for both solvents. There is another acidity function, J_0 or C_0,[5b] which applies to equilibrium formation of carbonium ions from neutral molecules, but for unimolecular acid-catalysed reactions in which a carbonium ion is formed slowly, and converted rapidly into products, the correlation between rate and acidity is usually with the Hammett function h_0 (cf. ref. 9). In some cases this may be because, in the acidity ranges studied, H_0 and J_0 do not diverge sufficiently, but it seems that in many cases the energy maximum in the reaction path is reached for rather small bond extensions,[10] and that therefore the appropriate acidity function is that applying to protonation of a neutral base. Where the carbonium ion is in equilibrium with the reactants the rate correlates with $-$antilog J_0.[11]

The H_0 scale gives the relative protonating powers of various acidic solutions, and from the Zucker–Hammett hypothesis, the rate of an A-1 reaction should depend only upon H_0, and not upon the particular acid or solvent.[5a,b] In fact the correlation between rate and Hammett acidity for A-1 reactions in different solvents is sometimes bad, even though the correlation for a particular solvent may be good, *e.g.*, the rate of hydrolysis of sucrose correlates well with h_0 for changes of acidity in a given solvent, but badly if comparison is made between different solvents.[4] The relation between Hammett acidity and the first-order rate constant, k, for an A-1 reaction of a neutral compound S, is:

$$k \propto a_{H^+} . f_S/f_{H^+S} \propto h_0 \text{ (when } f_S/f_{H^+S} = f_B/f_{H^+B})$$

This equality of the ratios of activity coefficients may hold for aqueous solutions of varying concentration, but it is more likely to fail with drastic changes in the medium, by addition of a neutral salt, or an organic solvent. A breakdown of this relationship is most likely when the structures of the indicator base, B, and the reactant, S, are very different,[12] as for aromatic amines and sucrose. It should be less likely to fail for reactions of 4-methoxydiphenylmethanol, because the geometry of this compound is not very different from those of aromatic amines, and here the correlation between rate constant and h_0 is good, for changes in medium as well as acid concentration. This is shown in Fig. 1. The slope is greater than unity, but this is quite common for reactants with molecular sizes similar to that of 4-methoxydiphenylmethanol. It is very similar to that observed for the hydrolysis of 4-methoxydiphenylmethyl acetate in aqueous dioxan by mechanism $A_{AL}1$.[7b]

It is, however, possible that this high slope comes about because the appropriate acidity function for kinetic comparison is J_0. This possibility has been considered for the racemisation and oxygen exchange of 1-phenylethanol.[2] Unfortunately we have no values for J_0 in acid aqueous dioxan, although this acidity scale should increase more rapidly with increasing acid concentration than does H_0, and the values of H_0 and J_0 would not be expected to coincide in the different aqueous dioxan solvents, with their different water contents. The points of Fig. 1 show some divergence from a straight line, but this is probably because of experimental uncertainties in H_0, which are largest at low acidities, and in the rate constants at high acidities where the half-life is *ca.* 1 min. This is particularly serious for experiments in the more aqueous solvent where low solubility restricts the precision of the kinetic measurements.

Experimental

Materials.—The solvent for most of the experiments was aqueous dioxan made up by mixing appropriate volumes of purified dioxan and water.

Acid solutions were made up by mixing 72% " AnalaR " perchloric acid with the aqueous

[9] Deno and Perizollo, *J. Org. Chem.*, 1957, **22**, 836.
[10] Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979.
[11] Bethell and Gold, *J.*, 1958, 1905.
[12] Deno and Perizollo, *J. Amer. Chem. Soc.*, 1957, **79**, 1345.

XUM

dioxan solvent, and adding purified dioxan sufficient to restore the ratio of dioxan to water.[4] The acid concentration was checked by acid–base titration at the beginning or end of the run.

4-Methoxydiphenylmethanol, prepared and resolved by the original procedures,[12] was supplied by Professor A. N. Bourns; it had $[\alpha]_D^{25} = -7{\cdot}8°$ (in CS_2). Isotopically labelled alcohol enriched in the hydroxylic oxygen atom, and prepared by hydrolysis of the chloride in ^{18}O-containing water, was similarly obtained. It contained 0·98 atom % excess of ^{18}O.

The isotopic abundance of the hydroxylic oxygen atom was determined by a method devised with Professor A. N. Bourns. A known amount of the alcohol was heated in a sealed tube with a known amount of carbon dioxide for 24 hr. at 250°. One mol. is eliminated from 2 mol. of the alcohol, and this water is allowed to equilibriate its oxygen atom with those of the carbon dioxide. The total isotopic abundance, N_t, of the carbon dioxide is given by $N_t = 100/(2KR + 1)$ atom % (where R is the ratio of masses 44 : 46, and $K = 1{\cdot}038$). The excess abundance is then calculated by subtracting the abundance of isotopically normal carbon dioxide. The excess of isotopic abundance of the water (and therefore of the alcohol) is then calculated from the excess abundance of the carbon dioxide and the known amounts of alcohol and carbon dioxide present initially. This neglects any isotopic fractionation in the thermal dehydration of the alcohol.

Kinetics of Oxygen Exchange.—In dioxan–water (60 : 40 v/v) samples of the isotopically enriched alcohol (*ca.* 0·1 g.) were dissolved by shaking them in 5 c.c. of the acid solvent, which was at the temperature of the thermostat. After the appropriate reaction time sufficient 5% sodium hydroxide was added to neutralise the acid and so stop the exchange. The alcohol was extracted with ether, the ether evaporated under reduced pressure, and the alcohol dried in a desiccator. The alcohol was finally purified by vacuum sublimation at 75—80°, and its purity checked by m. p. The recovery of alcohol was between 80 and 95%. The isolation procedure does not change the isotopic enrichment, or the rotation of the alcohol.

The time of dissolution was sufficiently short for this procedure to be used for most of the exchange experiments in this solvent. However, the exchange in 0·936M-perchloric acid is too fast for this procedure to be used, and here samples of the alcohol (0·1 g.) were first dissolved in the purified dioxan. This solution and the aqueous acid were brought to thermostat temperature and then mixed. The reaction was stopped by addition of alkali and the alcohol isolated as described.

Oxygen Exchange in Dioxan–Water (40 : 60 *v/v*).—The procedure was that described above for the run in dioxan–water (60 : 40 v/v) and 0·936M-perchloric acid, except that samples of *ca.* 0·1 g. in 20 c.c. of solvent were used.

This procedure could not be used for the fastest run in this solvent (with 0·63N-perchloric acid) because here the time of mixing the solutions was becoming appreciable relative to the half-life, and this time of mixing could differ for the various points of the run. Therefore the isotopically enriched 4-methoxydiphenylmethanol was dissolved in 40·0 c.c. of purified dioxan and this and 63·0 c.c. of 1·04M-aqueous perchloric acid were brought to thermostat temperature. The two solutions were mixed rapidly, giving a solution of 0·63M-perchloric acid (checked by titration). At appropriate times aliquot portions were removed, and the acid was neutralised and the alcohol extracted and purified as already described.

Miscellaneous Exchange Experiments in Water.—Optically active 4-methoxydiphenylmethanol is racemised in boiling water, in which it is slightly soluble.[13] This racemisation may be a spontaneous transformation of the neutral alcohol molecule, or it may be catalysed by the protons generated by autoprotolysis of water, or by the small amounts of carbon dioxide present. The oxygen exchange under these conditions was therefore studied.

Isotopically labelled alcohol (0·25 g.) was added to boiled and thoroughly degassed distilled water (500 c.c.), in a flask with its ground-glass stopper sealed with a high-vacuum Silicone grease. The flask was heated to 100°, and most, but not all, of the alcohol dissolved with thorough shaking. On cooling, the alcohol separated and was extracted with ether and purified as above. After being heated for 42 hr. the alcohol had exchanged 57% of its hydroxylic oxygen atoms with the water; in a second experiment under similar conditions there was 19% of exchange after 10 hours' heating.

Similar experiments were carried out with sodium hydroxide added to the solution. With 0·1M-sodium hydroxide, and the solution not degassed, there was <2% of exchange after heating for 48 hr. at 100°. In a second experiment with M-sodium hydroxide, 10 hours' heating

[13] Balfe, Doughty, Kenyon, and Poplett, *J.*, 1942, 605.

at 100° gave <4% of exchange. It seems that the addition of hydroxide suppresses an acid-catalysed oxygen exchange, and it is therefore possible that the racemisation observed by Kenyon and his co-workers was also acid-catalysed.

Kinetics of Racemisation.—In dioxan–water (60 : 40 *v/v*). The solubility of the alcohol in this solvent is sufficient for the run to be followed directly in a 2 dm. jacketed polarimeter tube kept at 25·0° by circulating water. The solutions were made up as for the exchange runs. For the run with 0·101M-perchloric acid it was possible for 8—12 readings of the rotation to be taken for each point.

The rate of racemisation with $[HClO_4] > 0{\cdot}1$M was such that it was difficult to take a large number of points at any given time. Therefore a large number of individual readings of the rotation were taken; the logarithms of these observed rotations are plotted against time for one run in Fig. 2.

In dioxan–water (40 : 60 *v/v*). The low solubility of the alcohol in this solvent made it necessary to isolate and purify the alcohol, for each individual point of the run, by the procedure described for the exchange experiments in this solvent. The rotations of these isolated samples were then determined in carbon disulphide, using a 2 dm. micropolarimeter tube holding about 3 c.c. of solution.

The first-order rate constants were calculated graphically, for exchange by plotting the logarithm of the excess isotopic abundance, *N*, against time, and for racemisation by plotting the logarithm of the rotation (or the specific rotation where appropriate) against time.

Examples of the results obtained are shown in the Table 2 and in Fig. 2.

TABLE 2. *Racemisation in dioxan–water* (40 : 60 *v/v*) *at* 25°.

$[HClO_4] = 0{\cdot}530$M. 0·04—0·09 g. of material was isolated for each point of run. Specific rotation measured in CS_2.

Time (min.)	0	1·0	2·0	3·0 *		6·0
$[\alpha]_D^{25}$	−7·3	−5·8	−4·8$_5$	−4·7$_5$	−4·3	−2·2

* Separate samples.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1.

[*Received, June 20th,* 1958.]

---

958. *Nucleophilic Displacements in Organic Sulphites. Part I. The Positions of Bond Fission in the Hydrolyses of Some* 1 : 2- *and* 1 : 3- *Cyclic Sulphites.*

By C. A. BUNTON, P. B. D. DE LA MARE, (MISS) P. M. GREASELEY, D. R. LLEWELLYN, N. H. PRATT, and J. G. TILLETT.

The positions of bond-fission in the hydrolyses of ethylene sulphite, propylene sulphite, *meso*-2 : 3-butylene sulphite, tetramethylethylene sulphite, trimethylene sulphite, and 1 : 3-butylene sulphite have been determined isotopically under acidic and alkaline conditions. Sulphur–oxygen bond-fission occurs in all the examples studied. It has been shown, for ethylene and for trimethylene sulphite, that the organic sulphite, originally isotopically normal, is still normal when recovered after partial hydrolysis in isotopically enriched water under either acidic or alkaline conditions.

GARNER and LUCAS [1] showed that the formation, followed by the acid- or alkali-catalysed hydrolysis, of 2 : 3-butylene sulphite proceeded without change in the optical activity of the butane-2 : 3-diol used as starting material. They concluded that these hydrolyses proceed with sulphur–oxygen bond-fission. Foster, Hancock, and Overend [2] have studied the hydrolyses of the cyclic sulphites of the *cyclo*hexane-1 : 2-diols. The *trans*-isomer gave the *trans*-diol; the *cis*-isomer gave the *cis*-diol in acidic solution, and mainly the *trans*- with some *cis*-diol, in alkaline solution. From this they concluded that some

[1] Garner and Lucas, *J. Amer. Chem. Soc.*, 1950, **72**, 5496.
[2] Foster, Hancock, and Overend, *Chem. and Ind.*, 1956, 1144.

XUM

carbon–oxygen bond-fission occurs under the latter conditions. Other cases are known in which the products of reaction with nucleophilic reagents require the conclusion that carbon–oxygen bond fission has occurred, at least as part of the total reaction. Thus the reactions of ethylene sulphite with aryloxide ions [3] can lead to the formation of products of the type $ArO{\cdot}CH_2{\cdot}CH_2{\cdot}OH$, and dialkyl sulphites can undergo cleavage with iodide ions in acetone [4] forming, among other products, alkyl iodides.

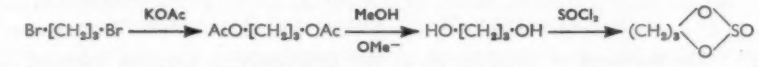
A preliminary account has been given [5] of the establishment, by using ^{18}O as tracer, that sulphur–oxygen bond-fission occurs in the acid- and alkali-catalysed hydrolyses of ethylene sulphite in water. These measurements have now been extended to other sulphites as part of a programme in which we seek to establish the range of conditions over which the various mechanisms available operate.

Experimental

The cyclic sulphites were prepared mostly by standard methods.[cf. 6] Ethylene sulphite had b. p. 88°/52 mm., n_D^{25} 1·4450; propylene sulphite, b. p. 58°/9 mm., n_D^{25} 1·4359. For the preparation of *meso*-2 : 3-butylene sulphite, a commercial specimen of butane-2 : 3-diol, containing much of the *meso*-isomer, was fractionated. The final fractions, b. p. 127°/101 mm., n_D^{25} 1·4370, were converted into the sulphite, which was fractionally distilled in a helix-packed 3 ft. column. Initial fractions were still slightly optically active, but the later fractions had no optical activity, and had b. p. 67°/8 mm., n_D^{25} 1·4380. Tetramethylethylene sulphite was prepared by Szmant and Emerson's method.[7] The product, recrystallised first from methanol and finally from light petroleum (b. p. 40—60°), had m. p. 44—45°, *M* (by hydrolysis with excess of alkali), 162 (calc. 164). The infrared spectrum of this and of *meso*-2 : 3-butylene sulphite, determined by using a Grubb-Parsons double-beam infrared spectrophotometer, had absorption bands respectively at 709, 773, 799, 892, 970, 1131, 1167, 1221 cm.$^{-1}$; and at 662, 671, 691, 729, 801, 833, 905, 992, 1017, 1099, 1143, 1167, 1206, 1353, 1393, 1449, 1468 cm.$^{-1}$.

Although trimethylene sulphite, whether prepared from propane-1 : 3-diol which had been fractionally distilled or from a commercial specimen, appeared to be homogeneous from its b. p. and its rate of hydrolysis under acid conditions, it contained impurities which were very difficult to remove. These were shown to be sulphites derived from impurities in propane-1 : 3-diol. This material, even after careful fractional distillation, contained 30%, calculated as propane-1 : 2-diol, of material oxidisable by periodic acid by the method described by Jackson.[8] Some of this may have been propane-1 : 2-diol; some was probably dihydroxyacetone or glyceraldehyde, since the infrared spectrum had a strong maximum at 1727 cm.$^{-1}$, indicating the presence of a C=O group. A similar absorption band appeared in the spectrum of the derived sulphite.

Finally, trimethylene sulphite was prepared by the sequence:



The trimethylene bromide was fractionally distilled and had b. p. 163°/760 mm., n_D^{24} 1·5215. The derived diacetate had b. p. 127°/50 mm., n_D^{25} 1·4171. The derived propane-1 : 3-diol was a colourless liquid, b. p. 113°/15 mm., n_D^{25} 1·4373; its infrared spectrum had no absorption at 1727 cm.$^{-1}$. Reaction with excess of periodic acid showed the presence of 2·1% of 1 : 2-diol. The sulphite prepared from it had b. p. 89°/39 mm., n_D^{25} 1·4509. Since the yields of cyclic sulphite are considerably greater from 1 : 2- than from 1 : 3-diols, it is to be expected that the derived sulphite might contain rather more impurity from the former material, as proved to be so. The diol produced by hydrolysis of our best sample of trimethylene sulphite contained 4·7% of 1 : 2-diol as determined by reaction with excess of periodic acid.

Similar difficulties were experienced in preparing pure 1 : 3-butylene sulphite. Butane-1 : 3-diol (1 : 2-diol, by reaction with periodic acid, 2·3%) gave a sulphite, b. p. 54°/6 mm., n_D^{25} 1·4430, which contained 3·7% of 1 : 2-sulphite.

[3] Carlson and Cretcher, *J. Amer. Chem. Soc.*, 1947, **69**, 1953.
[4] Foster, Hancock, Overend, and Robb, *J.*, 1956, 2589.
[5] Bunton, de la Mare, Llewellyn, Pearson, and Pritchard, *Chem. and Ind.*, 1956, 490.
[6] de la Mare, Klyne, Millen, Pritchard, and Watson, *J.*, 1956, 1813.
[7] Szmant and Emerson, *J. Amer. Chem. Soc.*, 1956, **78**, 454.
[8] Jackson, *Organic Reactions*, 1944, **2**, 341.

Position of Bond-fission.—Hydrolysis in alkaline solution. A procedure similar to that given below for trimethylene sulphite was followed. The sulphite (*ca.* 20 g.) was added slowly to enriched water (100 ml.) containing 2 equiv. of sodium hydroxide. The reaction was completed by heating the mixture to 100° for 4 hr. Most of the water was then removed by fractional distillation, first through a fractionating column and then under high vacuum. Finally the diol was evaporated under the vacuum provided by a mercury-vapour pump, and collected in a cooled trap. Benzene (25 ml.) was added to the distillate and the mixture was distilled. This procedure was repeated until the distillate was clear. The residue (usually *ca.* 5 ml.) was redistilled at a pressure of *ca.* 10 mm.; first and last fractions were rejected. The resulting product had the correct refractive index, and was used for isotopic analysis. Hydrolyses of the 1 : 2-sulphites were complete in ½ hr. at room temperature.

Hydrolysis in acid solution. The following method was used for trimethylene sulphite, and with slight modification was satisfactory for the other cyclic sulphites. The sulphite (*ca.* 20 g.) was heated under reflux for about 8 hr. with enriched water (100 ml.) and perchloric acid (usually 0·2—0·5M), a stream of nitrogen being passed through the solution continuously to remove the liberated sulphur dioxide. The resulting solution was neutralised (phenolphthalein), and the diol was recovered as described above.

Isotope Analysis.—The diol was pyrolysed to carbon monoxide on red-hot carbon at low pressure in a radio-frequency heater. The carbon monoxide was analysed mass-spectrometrically. The results, both for acidic and for alkaline hydrolysis, are given in Table 1.

TABLE 1. *Hydrolysis of cyclic sulphites in isotopically enriched water.*

	^{18}O-Abundance (atoms % excess)			
	Alkaline hydrolysis		Acidic hydrolysis	
Sulphite	H_2O (solvent)	Diol (recovered)	H_2O (solvent)	Diol (recovered)
Ethylene	0·410	0·005	0·300 *	0·006 *
	0·860	0·000	0·935 †	0·001 †
Propylene	0·663	0·003	0·350	0·000
meso-2 : 3-Butylene	0·395	0·000	0·350	0·033
Tetramethylethylene	0·935	0·011	0·600	0·024
Trimethylene	0·365	0·002	0·966	0·015
1 : 3-Butylene	0·350	0·001	0·350	0·025

* With 2·0M-$NaClO_4$ and 0·5M-$HClO_4$. † With 6·0M-HCl.

TABLE 2. *Isotopic analyses of sulphites recovered after partial hydrolyses.*

			^{18}O-Abundance (atoms % excess) *	
Experiment	Sulphite	Conditions	H_2O (solvent)	Sulphite (recovered)
(*a*)	Ethylene	Alkaline	0·940	0·016
(*f*)	Ethylene	Alkaline †	0·000	0·052
(*c*)	Ethylene	Acidic	1·07	0·016
(*d*)	Ethylene	Acidic	0·997	0·000
(*e*)	Ethylene	Initially neutral	0·997	−0·004
(*b*)	Trimethylene	Alkaline	0·997	−0·002

* Relative to a sample of carbon monoxide obtained by pyrolysis of oxalic acid.
† In this experiment, the sulphite (^{18}O-abundance, 0·055 atom % excess) was enriched isotopically on the exocyclic oxygen atom.

Recovery, and Isotopic Analysis, of Sulphites after Partial Reaction.—Since isotopic exchange between the oxygen atom of the S=O group and the solvent is a possible process with important mechanistic consequences, experiments were performed to test whether this exchange occurred. (*a*) Ethylene sulphite (9·8 g.) was allowed to react with sodium hydroxide (3·7 g., the amount required for decomposition of half of the sulphite) in $H_2{}^{18}O$ (100 ml.). When reaction was complete, the ethylene sulphite was recovered by extraction with ether and fractional distillation. The product had b. p. 58°/8 mm., n_D^{25} 1·4446, and the isotopic abundances are shown in Table 2. Similar experiments were performed (*b*) for trimethylene sulphite; (*c*), (*d*) for ethylene sulphite in 0·1M-perchloric acid, the reaction mixture being allowed to stand at 73° for approximately one half-life; and (*e*) in initially neutral solution. A final check (*f*) was made by preparing ^{18}O-labelled ethylene sulphite. Sulphur dioxide was bubbled into enriched water,

XUM

to give an aqueous solution of $S^{18}O_2$. This was heated, and the $S^{18}O_2$ was passed into phosphorus pentachloride. The mixture was fractionally distilled, to give $S^{18}OCl_2$, b. p. 78°. From this was prepared by the usual method ^{18}O-labelled ethylene sulphite. This was treated with sufficient alkali to hydrolyse half of it in isotopically normal water, and the recovered sulphite was examined. The results of these isotopic analyses are also given in Table 2; values for the sulphites were determined by passing the sulphite through a red-hot carbon tube heated *in vacuo* by a radio-frequency furnace. This procedure differed from that normally used in that there was no liquid-nitrogen trap in the vacuum system. Thus oxides of sulphur formed by decomposition were not removed by condensation, but were reduced by the carbon. We know that this method can detect ^{18}O-labelling of the sulphur-oxygen atom but we have no guarantee that it can do this quantitatively.

Discussion

In all the reactions studied, whether under acidic or alkaline conditions, the diol produced in reaction in isotopically enriched solvent was isotopically normal. Hence sulphur–oxygen bond-fission occurs in all these cases, even under alkaline conditions with ethylene sulphite, structurally the most favourable situation for bimolecular attack on carbon; and under acidic conditions with tetramethylethylene sulphite, structurally the most favourable situation for unimolecular C–O heterolysis.

The exchange reaction of the type shown in the equation does not occur in significant competition with the hydrolysis, either under acidic or alkaline conditions, with either ethylene or trimethylene sulphite.

Elucidation of the mechanisms prevailing in these reactions requires consideration also of the kinetics of hydrolysis: these are described in the accompanying papers.

We thank Mr. P. Chaffe for technical assistance.

William Ramsay and Ralph Forster Laboratories,
University College, Gower St., London, W.C.1. [*Received, July 30th*, 1958.]

---

959. *Nucleophilic Displacements in Organic Sulphites. Part II.*[1] *The Acid-catalysed Hydrolysis of Ethylene Sulphite and of Trimethylene Sulphite.*

By C. A. Bunton, P. B. D. de la Mare, and J. G. Tillett.

The hydrolysis of ethylene sulphite and of trimethylene sulphite are catalysed by mineral acids. At concentrations of perchloric acid greater than about 1M, the rates increase with acidity more rapidly than does the stoicheiometric concentration of acid. The rates are, however, closely proportional to the stoicheiometric acidity when the total concentration of electrolyte is kept constant by addition of sodium perchlorate; in the presence of added neutral salts, the rates are not proportional to the acidity as measured by Hammett's acidity function, h_0. Nucleophilic anions catalyse the hydrolysis. Some aspects of the mechanistic paths consistent with these experimental features are discussed.

In Part I[1] it was shown that the acid-catalysed hydrolyses of a number of cyclic sulphites proceed with S–O bond-fission. Preliminary measurements of the kinetics of these reactions have been referred to elsewhere;[2] the present paper amplifies these measurements

[1] Part I, Bunton, de la Mare, Greaseley, Llewellyn, Pratt, and Tillett, *J.*, 1958, preceding paper.
[2] Bunton, de la Mare, Llewellyn, Pearson, and Pritchard, *Chem. and Ind.*, 1956, 490.

in the cases of ethylene and trimethylene sulphites, which serve as the simplest examples of 1 : 2- and of 1 : 3-sulphites.

Experimental

The properties of the cyclic sulphites are recorded in Part I.[1] The acids were of Analytical Reagent quality. Their concentrations were determined in the reaction mixtures by titration with standard alkali. Sodium chloride and sodium bromide were dried at 120°. Sodium perchlorate was dried for 4 days at 120°; it was free from halide. Sodium toluene-*p*-sulphonate was a commercial recrystallised specimen. Tetraethylammonium perchlorate was prepared from tetraethylammonium hydroxide by neutralisation with perchloric acid. The precipitate was washed with water until the washings were neutral, then dried at 100°.

The rates of hydrolysis were determined by a conventional sealed-tube method. The conversion of organic sulphite into sulphur dioxide was determined at intervals by breaking samples under excess of standard iodine solution, which was then back-titrated with sodium thiosulphate. The following exemplifies a typical kinetic run, for 0·036M-ethylene sulphite

Time (min.)	0	7	14	21	28	35	42	50
Titre (ml. 0·0100N-iodine) ...	7·44	9·64	11·69	13·77	15·46	17·65	18·56	20·21
10^3k_1 (min.$^{-1}$)	—	1·17	1·17	1·22	1·20	1·20	1·20	1·21
Time (min.)	60	75	90	120	180	∞		
Titre (ml. 0·0100N-iodine) ...	22·03	24·13	26·04	28·77	32·35	35·53		
10^3k_1 (min.$^{-1}$)	1·22	1·20	1·21	1·19	1·21	—		

in 1·098M-perchloric acid with 0·25M-sodium chloride at 44·6°. The finite titre for time $t = 0$ represents reaction during the time allowed for warming of the samples to the temperature of the thermostat. Values of k_1 were calculated from $k_1 = 2{\cdot}303[\log a/(a - x)]/t$, where a is the molarity of organic sulphite at time $t = 0$, and x is the molarity of sulphur dioxide liberated at time t. Calculated (35·68) and observed infinity values agreed within experimental error. The fact that the first-order rate-coefficients calculated by the use of the above formula are substantially constant over considerably more than 50% of reaction implies that one mole of material behaving on titration as sulphur dioxide is liberated for each mole of organic sulphite decomposed.

The results are summarised in Tables 1 and 2. Rates are corrected, where the correction is significant, for the rate in neutral solution. Values of H_0 are included for reference, mostly from Long and Paul's review.[3] That for hydrogen bromide has recently been determined by Vinnik, Krugslov, and Chirkov.[4]

Discussion

The kinetic forms observed for ethylene and for trimethylene sulphite are so similar that illustrations for most of the ensuing discussion could be taken from the data for either compound. Many acid-catalysed reactions fall into one of two classes, according to whether the rate of the reaction is proportional to the acidity as measured by the degree of protonation of a weak nitrogen base under the same conditions (*i.e.*, to Hammett's acidity function, h_0) or to the stoicheiometric concentration of acid.[3] In the following discussion, the former class will be described as Hammett-dependent, and the latter as concentration-dependent.

Correlation of Rate with Hammett's Acidity Function.—In Fig. 1 are plotted the logarithms of the rates of hydrolysis of ethylene sulphite against values[3,4,5] of Hammett's acidity function, in its logarithmic form, H_0. The reaction has been followed well into the region of acidity in which h_0 and $[HClO_4]$ are markedly different. Only the effects of variation in the concentration of perchloric acid being considered first, the values lie near to a straight line of slope 0·68, though the graph shows an appreciable curvature, particularly at the higher acidities. A straight line of nearly unit slope would be expected

[3] Long and Paul, *Chem. Rev.*, 1957, **57**, 1.
[4] Vinnik, Krugslov, and Chirkov, *Zhur. fiz. Khim.*, 1956, **30**, 827.
[5] McIntyre and Long, *J. Amer. Chem. Soc.*, 1954, **76**, 3240.

XUM

Table 1. *First-order rate-coefficients (min.$^{-1}$) and related data for hydrolysis of ethylene sulphite in water (concentrations in moles l.$^{-1}$).*

(*a*) *At* 44·6°.

$HClO_4$	0	0·030	0·060	0·150	0·350	0·500
10^4k_1	0·065	1·35	2·79	6·89	16·9	25·9
$10^3k_1/H^+$	—	4·50	4·65	4·55	4·80	5·18
H_0	—	1·52	1·22	0·82	0·46	0·31
$HClO_4$	1·098	1·500	2·184	3·275	4·373	5·481
10^4k_1	58·6	83·5	141 *	287	476	898
$10^3k_1/H^+$	5·34	5·56	6·46	8·76	8·80	16·22
H_0	−0·13	−0·44	−0·72	−1·21	−1·74	−2·31

* In 90% D_2O, 10^4k_1 = 213 min.$^{-1}$.

(*b*) *At* 44·6°, *with added sodium perchlorate.*

$HClO_4$ ...	0·500	1·000	2·000	3·000
$NaClO_4$ ...	5·500	5·000	4·000	3·000
10^4k_1	78·6	185	397	610
$10^3k_1/H^+$	15·7	18·5	19·3	20·3
H_0	−1·00	−1·31	−1·73	−2·00

(*c*) *At* 44·6°, *with other acids.*

Acid ...	1·226M-H_2SO_4	1·80M-H_2SO_4	0·500M-HCl
10^4k_1 ...	128	235	65·6
H_0	−0·26	−0·59	+0·31
Acid.....	1·00M-HCl	1·30M-HCl	1·30M-HBr
10^4k_1 ...	208	382	*ca.* 1000
H_0	−0·13	−0·24	−0·24

(*d*) *At* 44·6°, *with added sodium chloride,* 0·25M.

$HClO_4$	1·098	2·184	3·275	4·373	1·000
$NaClO_4$	—	—	—	—	5·000
10^4k_1	120	323	742	1760	608

(*e*) *At* 73·05°.

$HClO_4$	0·108	0·270	0·432	0·539	1·078	2·156
10^4k_1	81·8	202 *	314	380	874	2030
$10^3k_1/H^+$	75·9	74·8	72·7	70·5	81·1	94·2

* In 90% D_2O, 10^4k_1 = 332 min.$^{-1}$.

(*f*) *At* 73·05°, *with* 0·270M-*perchloric acid.*

$NaClO_4$	0·000	0·500	1·000	2·000	3·000	4·000
10^4k_1	202	217	257	302	356	440
NaCl	0·000	0·050	0·100	0·200	0·300	
10^4k_1	202	241	278	354	443	
NaBr	0·000	0·030	0·100	0·200		
10^4k_1	202	234	314	438		
$C_7H_7SO_3Na$	0·000	0·500	1·000	1·500		
10^4k_1	202	218	228	242		

(*g*) *At* 73·05°, *with* 0·108M-*perchloric acid.*

NaCl	0·000	0·300	0·400	0·600	0·800	1·000
10^4k_1	81·8	110	187	237	290	342

(*h*) *At* 73·05°, *with* 0·284M-*perchloric acid and* 0·47M-*tetraethylammonium perchlorate,* 10^4k_1 = 185 *min.*$^{-1}$; *with* 0·27M-*perchloric acid and* 0·41M-*tetraethylammonium perchlorate,* 10^4k_1 = 217 *min.*$^{-1}$.

Table 2. *First-order rate-coefficients for the hydrolysis of trimethylene sulphite in water (units as in Table* 1).

(*a*) *At* 35·0°.

$HClO_4$	0·515	1·03	1·55	2·07	3·09	4·12
10^4k_1	40·7	88·0	150	239	447	989
$10^3k_1/H^+$	7·90	8·55	9·66	11·55	14·48	24·05
H_0	0·31	−0·08	−0·46	−0·67	−1·12	−1·61

(*b*) *At* 35·0°, *with added sodium perchlorate.*

$HClO_4$ ...	0·000	1·000	2·000	3·000	4·000
$NaClO_4$ ...	4·000	3·000	2·000	1·000	0·000
10^4k_1	0	186	392	670	910
$10^3k_1/H^+$	0	18·6	19·6	22·3	22·8

(*c*) *At* 60·0°.

$HClO_4$	0·206	0·309	0·412	0·515
10^4k_1	195	255	365	485
$10^3k_1/H^+$ ...	94·6	82·5	88·6	94·1

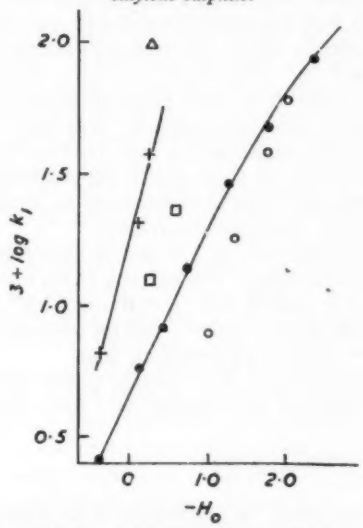
(*d*) *At* 60·0°, *with* 0·412M-*perchloric acid.*

$NaClO_4$	0·000	1·000	2·000	3·000
10^4k_1	365	499	628	741
NaCl	0·000	0·100	0·200	0·300
10^4k_1	365	495	633	788

NaBr	0·000	0·030	0·100	0·200
10^4k_1	365	442	577	778
$C_7H_7SO_3Na$	0·000	1·000	1·500	
10^4k_1	365	450	486	

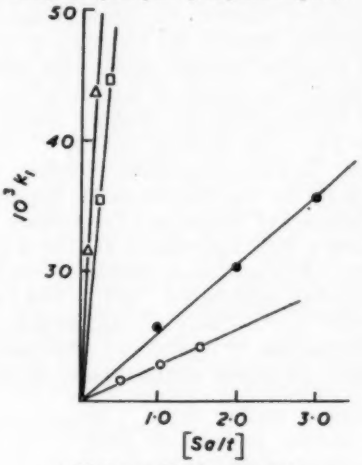
for a Hammett-dependent reaction. Appreciable deviations from this ideal behaviour have, however, been observed for reactions which are accepted as falling into this class.[3] It seems essential, therefore, to use some further criterion to decide whether the reaction now investigated is to be considered as Hammett-dependent. Such a criterion is provided by the influence of added salts. When, at high acidities, the stoicheiometric concentration of acid is kept constant and sodium perchlorate is added, the acidity of the solution as measured by H_0 is very considerably increased.[5] The rates of these acid-catalysed hydrolyses of sulphites are, however, not increased to nearly the same extent: This result is shown in Fig. 1; the full circles refer to experiments in which sodium perchlorate has been added to perchloric acid to make the total concentration of perchlorate ion 6·0M; under these conditions, values of H_0 are known.[5]

FIG. 1. *Acid-catalysed hydrolysis of ethylene sulphite.*



● $HClO_4$, ○ $HClO_4$ + $NaClO_4$, □ H_2SO_4, + HCl, △ HBr.

FIG. 2. *Effect of added salts on the acid catalysed hydrolysis of ethylene sulphite.*



△ NaBr, □ NaCl, ● $NaClO_4$, ○ $C_7H_7SO_3Na$.

Correlation of Rate with Stoicheiometric Concentration of Acid.—The above results, in our view, provide satisfactory evidence that the reaction is not Hammett-dependent. Clearly, however, it is not, in the conventional sense, concentration-dependent either. The values shown in the Tables 1(*a*), 1(*c*), 2(*a*), and 2(*c*) illustrate that the values of k_1/H^+ rise; the factor is nearly three over a range of concentration of perchloric acid, 0·5—4M. If the reaction is carried out under conditions in which the ionic strength is kept constant by addition of sodium perchlorate, however, the rate is very nearly proportional to the concentration of perchloric acid. This is shown by the approximate constancy of the values of k_1/H^+ given in Tables 1(*b*) and 2(*b*).

Effects of Added Salts on the Rate of Hydrolysis.—The above facts suggest that the reaction is essentially concentration-dependent, with a superposed dependence on the concentration of added electrolyte. Since the concentrations involved are fairly high, it might be expected that the rate of the reaction would be affected in a specific manner by different electrolytes. One test of this hypothesis is shown in Fig. 1. The points which represent catalysis by added sulphuric, hydrochloric, and hydrobromic acids fall well above the plot of rate against concentration of perchloric acid; accordingly, at the

XUM

same molar concentration of acid, the four acids have widely different catalytic power for the hydrolysis [Table 1(*a*), (*c*)].

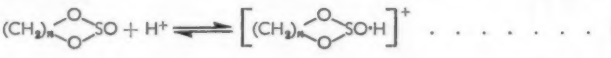
Catalysis of the reaction by added electrolytes is not confined to the region of high acidity. Fig. 2 illustrates this for various electrolytes.

The salts fall into two fairly well-defined classes. The first, in which the effects are small or zero, includes sodium perchlorate, sodium toluene-*p*-sulphonate, and tetraethylammonium perchlorate. The first two have a small accelerating power on the reaction, and the dependence of rate upon concentration of salt is linear, within experimental error, up to a concentration of *ca.* 2M. Tetraethylammonium perchlorate has very little effect on the rate.

The second class includes sodium chloride and sodium bromide. These salts have a very marked catalytic power, and the rate is very nearly proportional to the concentration of salt. Such catalytic power appears to be associated specifically with the negative ion, and this accords with the catalytic power of hydrogen chloride and of hydrogen bromide, illustrated in Fig. 1. Here it can be seen that, at high concentrations of acid, the points representing catalysis by these substances lie markedly above the plot representing the relationship between the logarithm of the rate and H_0. Still more, of course, do these acids exceed in catalytic power what would be expected from their molar concentrations, the results for perchloric acid at low acidity being taken as standard. Sulphuric acid must be included in this category, and the effects of the negative ions concerned fall in the order $Br^- > Cl^- \gg HSO_4^-(>ClO_4^-)$. This is the order of their decreasing nucleophilic power. It seems reasonable, therefore, to attribute this type of catalysis to nucleophilic attack by the negative ion on the sulphur atom of the protonated sulphite.

Influence of Solvent and Temperature.—The reaction, both at low and at high acidity, is faster in 90% D_2O than in H_2O by a factor of 1·5 or more. The entropy (ΔS^*) and the energy (ΔE) of activation, calculated from formula $k = (ekT/h) \exp(\Delta S^*/R) \exp(-\Delta E/RT)$ for ethylene sulphite are: ΔS^*, −15·8 e.u.; ΔE, 20·15 kcal. mole^{-1}; and for trimethylene sulphite: ΔS^*, −13·0 e.u.; ΔE, 20·15 kcal. mole^{-1}; both at 1M-perchloric acid.

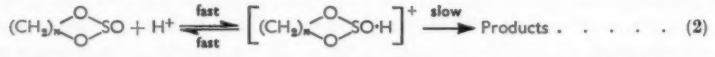
Mechanism of Hydrolysis; Preliminary Considerations.—The present paper records a study, by kinetic methods only, of this acid-catalysed ester-hydrolysis. From such a



. . . . . (1)

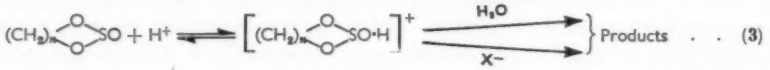
study, it is possible to make limited deductions concerning the mechanism of the reaction; the accompanying papers amplify the conclusions. The rate-difference in deuterated solvent and water is characteristic [5] of reactions which proceed by a pre-equilibrium proton-transfer, which in this case is probably (1). The proton might be associated either with the terminal or with the ring-oxygen atoms.

The reaction is not Hammett-dependent; therefore it is very unlikely that the stage of the reaction which follows the fast proton-transfer is a unimolecular reaction of the *A*-1 class, for such reactions are typically Hammett-dependent.[3, 5] So mechanisms of the type shown in equation (2) are eliminated.



. . . . . (2)

It seems probable, therefore, that some nucleophilic reagent is concerned in the rate-determining covalency change. The most obvious possibility is:



. . (3)

Such a mechanism would accord with the considerable catalytic power of added nucleophilic reagents such as bromide or chloride ions. It would accord also with the negative entropies

of activation obtained in the present examples. Such negative entropy factors are often observed [7] in acid-catalysed reactions in which a molecule of the solvent is kinetically concerned in the rate-determining stage of the reaction.

Reactions of the type shown in equation (3), with the solvent water acting as the nucleophilic reagent, should follow the kinetic form: [8]

$$\text{Rate} \propto [S][H^+]f_s a_w f_{H^+}/f^{\ddagger} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Here $f^{\ddagger}$ is the activity coefficient of the transition state, which contains S, H_2O, and a proton; a_w is the activity of water; and the other symbols have their customary significance. In some examples [8] of reactions considered to follow this path, the activity-coefficient ratio, $f_s a_w f_{H^+}/f^{\ddagger}$, is near unity in the critical experimental region, and hence the rate of reaction is linearly dependent on the concentration of acid, as is required by the Zucker–Hammett hypothesis.

Such a limiting situation is not achieved in the present experiments, and in many examples in the literature similar deviations from what might be called ideal behaviour in terms of the above hypothesis are found. Thus the rate of iodination of acetophenone [9] is accurately proportional to the concentration of acid only up to about 1·5M, and increases more rapidly than the acid-concentration when this is increased further. Similarly the rates of hydrolysis of both methyl formate and ethyl acetate [10] are not strictly proportional to the concentration of acid. In the present experiments, the rate of hydrolysis increases much more rapidly than would be expected if the rate was linearly dependent on concentration of acid, and in fact over a limited range of acidity there is an approximate dependence of rate on the square of the concentration of acid. If sodium perchlorate is added to keep the total concentration of electrolyte constant at 6M, the rate of hydrolysis is then linear with acidity in the range of acid concentration 1—6M. Hence in these particular mixtures the above activity-coefficient term is very nearly constant, though this is not so for mixtures of perchloric acid with salts other than sodium perchlorate.

In considering the effect of the ionic species on the activity-coefficient term, it should first be noted that the effects of added salts on the rate of hydrolysis do not correlate with their effects on the activity coefficient, f_s, of the organic sulphite, as measured by the solubilities of ethylene sulphite in solutions of electrolytes.[11] Both sodium perchlorate and sodium toluene-*p*-sulphonate have a "salting-in" effect on ethylene sulphite, and hence reduce its activity coefficient.[11] The increase in the rate of hydrolysis found when these salts are added cannot, therefore, be associated with an effect on the activity of the organic substrate. Nor can it be associated with a change in the activity of water, for this decreases [12] with increasing concentration of perchloric acid.

It seems in fact that the activity coefficient ratio, $f_s a_w f_{H^+}/f^{\ddagger}$, is modified by the presence of added electrolytes, by an amount which is to a first approximation proportional to the concentration of the electrolyte, but has a specific value for each particular electrolyte. The catalytic power observed in the present experiments is in the order: $NaClO_4 \sim C_7H_7SO_3Na \sim HClO_4 > NEt_4ClO_4$. For perchloric acid, in the range 0·5—5M, the magnitude of the increase in the value of k_1/H^+, and therefore of the activity-ratio term, for a given increase in concentration of electrolyte is of the same order of magnitude as that of the change in the mean ion activity coefficient of perchloric acid.[12,13] There is, however, no direct association of these quantities in the more dilute solutions.

[6] Wiberg, *Chem. Reviews*, 1955, **55**, 713.
[7] Long, Pritchard, and Stafford, *J. Amer. Chem. Soc.*, 1957, **79**, 2362.
[8] Chmiel and Long, *J. Amer. Chem. Soc.*, 1956, **78**, 3326; Long, Dunkle, and McDevitt, *J. Phys. Colloid Chem.*, 1951, **55**, 813, 829.
[9] Zucker and Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2791.
[10] Bell, Dowding, and Noble, *J.*, 1955, 3106.
[11] Davies and Tillett, *J.*, 1958, 4766.
[12] Robinson and Baker, *Trans. Proc. Roy. Soc. N.Z.*, 1946, **76**, 250.
[13] Markham, *J. Amer. Chem. Soc.*, 1941, **63**, 874.

XUM

Acid-dependence in the Chloride-catalysed Reaction.—If the Zucker–Hammett hypothesis be accepted, reactions which involve a molecule of water undergoing covalency change in the rate-determining stage of an acid-catalysed reaction are typically concentration-dependent, whereas reactions which involve in the rate-determining transition state only a neutral substrate and a proton are typically Hammett-dependent. It is of some interest, therefore, to investigate what happens to the form of the dependence of rate on acidity in the present example, when the molecule of water is replaced by chloride ions in the transition state for the hydrolysis. To examine this, the reaction has been studied in the region of relatively high acidity, with and without chloride ions, present in amount (0·25M) sufficient to increase considerably the rate of reaction, but insufficient, it is considered [cf. 3] to alter differentially the values of H_0 for the solutions. The following are values for the reaction catalysed by 0·25M-sodium chloride at different acidities,[2] it being assumed that the added chloride ions do not differentially affect the rate of attack by water on the protonated sulphite.

$HClO_4$ (M)	1·098	2·184	3·275	4·373	1·000
$NaClO_4$ (M)	—	—	—	—	5·000
H_0 *	−0·13	−0·72	−1·21	−1·74	−1·3
$2 + \log_{10}(\Delta k_1/Cl^-)$ (l. mole^{-1} min.$^{-1}$) †	0·390	0·862	1·261	1·711	1·24

* In the absence of added chloride ions.

† $\Delta k_1 = \{k_1(Cl^-) - k_1 \text{ (no } Cl^-)\}$, for otherwise the same experimental conditions; the data are given in Tables 1(*a*) and 1(*d*).

There is a fairly accurately linear relationship between $\log_{10}(\Delta k_1/Cl^-)$ and H_0, and the slope (0·82) is nearer to unity than is the case for the non-catalysed reaction. The point representing the effect of added sodium perchlorate on the acidity lies below that which would be predicted from the value of H_0 for this solution, but less markedly so than for the non-catalysed reaction. So the chloride-catalysed reaction falls much nearer to the Hammett-dependent category than does the non-chloride-catalysed reaction. The rate-equation that should be followed in the former case is:

$$\text{Rate} \propto [S][H^+][Cl^-]f_s f_{H^+} f_{Cl^-}/f^{\ddagger} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

For this to be Hammett-dependent, it is required that the ratio $f_s f_{H^+} f_{Cl^-}/f^{\ddagger}$ follow the protonation of a neutral indicator, and it is not, perhaps, surprising that, though this seems to be approximately true, the test of adding sodium perchlorate reveals significant deviations from exact accordance.

The present paper leaves undiscussed the questions of intervention of reversible or non-reversible stages involving the half-hydrolysed ester of sulphurous acid; and also of the position of bond-fission under the various conditions of catalysis. These matters, and further details of the reaction paths, are discussed in the accompanying papers.

We are indebted to Professor F. A. Long, of Cornell University, and to Professors E. D. Hughes, F.R.S., and Sir Christopher Ingold, F.R.S., for valuable discussion; also to the Department of Scientific and Industrial Research for a grant (to J. G. T.).

William Ramsay and Ralph Forster Laboratories,
University College, Gower St., London, W.C.1.

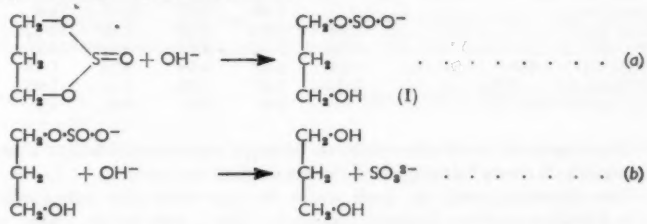
[*Received, July 30th*, 1958.]

960. *Nucleophilic Displacements in Organic Sulphites. Part III.* Comparison of Alkaline and Acidic Hydrolyses of Trimethylene Sulphite and Related Compounds.*

By C. A. Bunton, P. B. D. de la Mare, (Miss) A. Lennard, D. R. Llewellyn, R. B. Pearson, J. G. Pritchard, and J. G. Tillett.

Trimethylene and 1 : 3-butylene sulphites are hydrolysed in alkaline solution at rates which can be followed by conventional techniques at 0°. The reactions are of the second kinetic order, and have the same rates whether measured by the uptake of alkali or the liberation of sulphur dioxide. The possible intermediate (*e.g.*, $HO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}SO_2H$ or its anion) does not build up to high concentration during reaction. Alkyl substitution in the carbon chain seems to have little effect on the rate of alkaline hydrolysis, but 1 : 2-sulphites are in this process very much more rapidly hydrolysed. These results, in conjunction with studies of bond-fission (Part I) allow comparison with the corresponding data for acid-catalysed hydrolysis (Part II). In the latter reaction also, the possible intermediate does not build up in concentration; and alkyl substitution in the carbon chain has little influence on the rate, which now is little changed when the ring-size is altered.

The detailed courses of hydrolyses of cyclic sulphites, and the kinetic effects of structural changes, are considered. In contrast to the acid-catalysed hydrolyses of cyclic sulphites discussed in Part II, those in alkaline solution are very rapid. Possible stages in the reaction (*e.g.*, of trimethylene sulphite) are as follows:



Stages (*a*) and (*b*) have been shown both to involve sulphur–oxygen bond fission. In principle, either may be reversible, and either may be rate-determining.

The intermediate at the stage of half-hydrolysis would, if it were to accumulate during the reaction because the rate of stage (*b*) were similar to that of stage (*a*), be converted into its most stable prototropic form, (I), by rapid proton-transfer to and from oxygen. It is the anion of an acid of the type $RO{\cdot}SO_2H$, which would be expected to be similar in strength to sulphurous acid in its first dissociation ($K_a = 1{\cdot}7 \times 10^{-2}$). Sulphurous acid, produced in the second stage, is moderately strong in its first dissociation but weak in its second ($K_a = 1{\cdot}0 \times 10^{-7}$), so any build-up of the intermediate (I) could be measured by following the consumption of alkali with two indicators, to one of which sulphurous acid behaves as a monobasic acid (*e.g.*, Methyl Red) and to the other as a dibasic acid (*e.g.*, phenolphthalein).

Experimental

The materials have been described in the preceding papers.

Alkaline Hydrolyses.—Since trimethylene and 1 : 3-butylene sulphites still contained up to 5% of rapidly hydrolysed material derived from a 1 : 2-diol, the rates were measured with use of the first experimental point as the zero of time. The following are examples of typical kinetic runs.

Rate of liberation of sulphur dioxide. To 0·0328N-sodium hydroxide at 0° (100 ml.) was

* Parts I and II, preceding papers.

added trimethylene sulphite (1·0 ml., 0·2573M). Nitrogen was bubbled through the alkaline solution for 30 min. before the start, and was continued throughout to displace carbon dioxide. The solution was well shaken and at intervals samples (10 ml.) were pipetted into a mixture of 0·1N-hydrochloric acid (2 ml.) and 0·0100N-iodine in potassium iodide (25 ml.). The excess of iodine was then back-titrated with 0·01103N-sodium thiosulphate. The results are given in Table 1.

TABLE 1.

Time (min.)	0	0·75	1·38	2·38	3·34	4·38	6·32	infinity
Titre (ml.)	8·36	7·92	7·62	7·18	6·86	6·50	6·04	4·46
10^4x (M)	0	2·37	4·03	6·45	8·22	10·20	12·74	21·46
10^3[Sulphite] = $10^3(a-x)$ (M)	2·15	1·91	1·74	1·50	1·32	1·13	0·87	0·00
10^3[NaOH] = $10^3(b-2x)$ (M)	31·70	31·21	30·88	30·40	30·04	29·65	29·14	27·40
k_2 (l. mole^{-1} min.$^{-1}$)	—	4·9	4·8	4·8	4·7	4·8	4·7	—

Second-order rate-coefficients are calculated from $k_2 = 2{\cdot}303\{\log_{10}[a(b-2x)/b(a-x)]\}/t(b-2a)$ where a and b are the initial molarities of sulphite and alkali respectively, and x is the molarity of sulphite used up at time t, one mole of sulphite being assumed to liberate one mole of sulphur dioxide.

Rate of disappearance of alkali. The sulphite (1·0 ml., 0·2547N) was added to 0·0101N-sodium hydroxide (100 ml.), as described above, at 0°. At intervals samples (10 ml.) were withdrawn and quenched rapidly in excess of 0·00478N-hydrochloric acid (25 ml.) in stoppered flasks which had been bubbled out with nitrogen. The excess of acid was then back-titrated against 0·00470N-sodium hydroxide with a mixture of phenolphthalein and α-naphtholphthalein (referred to below as " phenolphthalein ") as indicator, titrations being carried out with a slow stream of nitrogen passing over the solution. Results are in Table 2.

TABLE 2.

Time (min.)	0	1·98	6·32	10·27	18·9	28·5	58·2	infinity
Titre (ml.)	6·06	6·86	8·00	8·80	10·62	11·69	13·27	15·28
10^4x (M)	0·00	1·85	4·55	6·40	10·70	13·20	16·95	21·50
10^3[NaOH] = $10^3(b-2x)$ (M)	9·29	8·92	8·38	8·01	7·15	6·65	5·90	4·99
10^3[Sulphite] = $10^3(a-x)$ (M)	2·15	1·97	1·70	1·51	1·08	0·83	0·46	0·00
k_2 (l. mole^{-1} min.$^{-1}$)	—	5·0	4·3	5·0	4·5	4·3	4·8	—

Measurements were also made in which a mixture of Methyl Red and Bromocresol Green (referred to later as " Methyl Red ") was used as indicator.

The formula used in both cases to calculate the rate-coefficients in Table 3 was $k_2 = 2{\cdot}303\{\log_{10}[a(b-2x)/b(a-x)]\}/t(b-2a)$. Iodometry was used unless otherwise specified.

TABLE 3.

10^3[Trimethylene sulphite] (M)	2·34	2·14	2·09	2·36	2·15[a]	1·76[b]	2·15		
10^3[Sodium hydroxide] (M)	19·4	9·55	40·4	10·1	9·29	10·2	31·7		
k_2 (l. mole^{-1} min.$^{-1}$)	5·0	4·7	4·9	4·6	4·7	4·7	4·8		
10^3[1 : 3-Butylene sulphite] (M)	2·27	2·20	2·24	2·22	2·26	1·91	1·99	2·11	2·05
10^3[Sodium hydroxide] (M)	10·02	20·02	10·01	9·98	10·04	36·2	63·4	77·2	98·2
k_2 (l. mole^{-1} min.$^{-1}$)	1·37	1·23	1·25	1·17	1·30	1·38	1·25	1·30	1·34

[a] Followed by acid–base titration with " phenolphthalein." [b] Followed by acid–base titration with " Methyl Red."

Acid Hydrolyses.—Experiments were made to compare the rates of hydrolysis of the various cyclic sulphites. The methods used are described in Part II. The following are results for catalysis by dilute sulphuric acid (<0·1M) at 100°:

Sulphite:	Ethylene	Propylene	3-Chloropropylene	1 : 3-Butylene
$k_1/[H^+]$ (l. mole^{-1} min.$^{-1}$)	0·72	0·70	0·22	1·70

The following are values of $10^2k_1/[H^+]$(l. mole^{-1} min.$^{-1}$) for hydrolyses catalysed by higher concentrations of perchloric acid at 35° (the value marked * is interpolated):

$HClO_4$ (M)	1	2	3	4	5	6
(−)2 : 3-Butylene sulphite	0·17	0·19	0·30	0·42	—	0·89
meso-2 : 3-Butylene sulphite	0·25	0·27	0·27	0·38	0·51	0·73
Tetramethylethylene sulphite	0·15*	0·17	0·20	0·26	0·38	—

XUM

These results for catalysis by perchloric acid show the increase of the second-order rate constant ($k_1/[H^+]$) with increasing acid concentration. This is similar to the kinetic form for the acid hydrolyses of ethylene and trimethylene sulphites (Part II). A few experiments were done with tetramethylethylene sulphite at 35° at an ionic strength kept constant ($\mu = 4$) by addition of sodium perchlorate to the perchloric acid. A linear relationship between k_1 and $[HClO_4]$ was observed (cf. Part II) (see Table 4).

TABLE 4.

$[NaClO_4]$ (M)	3·0	2·0	1·0	0·0
$[HClO_4]$ (M)	1·0	2·0	3·0	4·0
10^3k_1 (min.$^{-1}$)	0·25	0·47	0·72	1·05
$10^3k_1/[H]^+$ (l. mole^{-1} min.$^{-1}$)	0·25	0·24	0·24	0·26

The entropy and energy of activation for the acid-catalysed hydrolysis of tetramethylethylene sulphite were calculated from the rates in 1M-perchloric acid at 73·0° ($10^3k_1 = 5{\cdot}12$ l. mole^{-1} min.$^{-1}$) and at 35·0°: $\Delta S^* = -17{\cdot}8$ e.u., $E = 19{\cdot}7$ kcal. mole^{-1}. These values are very similar to those observed for the acid-catalysed hydrolyses of ethylene and trimethylene sulphites (Part II), and are in the range usually found for bimolecular acid-catalysed hydrolyses.[1]

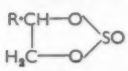
DISCUSSION

Alkaline Hydrolyses.—Alkaline hydrolyses of the 1 : 2-sulphites were too rapid for convenient kinetic measurement, but it is presumed that the same considerations apply to these as to the 1 : 3-sulphites. The latter are hydrolysed according to the kinetic form: $d[SO_2]/dt = k_2[\text{Sulphite}][OH^-]$, the assumption being made that for every mole of titratable sulphite formed, two moles of hydroxide ion were used up. The decrease in concentration of hydroxide ion, whether followed by titration of the remaining alkali to " Methyl Red " or to " phenolphthalein," obeyed the same law, and proceeded at the same rate, within experimental error, as the increase in concentration of sulphur dioxide followed by titration with iodine.

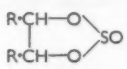
The significance of these results is as follows. The hydrolysis under alkaline conditions follows the sequence given earlier [reactions (*a*) and (*b*)].

If stage (*a*) were more rapid than stage (*b*), and were irreversible, the intermediate alkylsulphonate ion (I) would build up in concentration during reaction. If this intermediate did not react with iodine as sulphur dioxide does, then the rate of consumption of alkali could not equal the rate of liberation of material titratable with iodine. If, alternatively, the intermediate reacted with iodine as sulphur dioxide does, then different rates of disappearance of alkali would be observed, depending on which indicator was chosen for the titration. In fact, the liberation of material titratable with iodine, and the disappearance of alkali based on titration with either indicator, have the same rates. Hence the second stage of the reaction must be much more rapid than the first, and the intermediate (I) does not build up in concentration during the reaction.

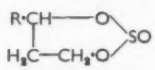
Another formally possible reaction scheme is that the intermediate (I) is in equilibrium with the reactants. This would give a rapid equilibration between the oxygen atoms of the SO_2 group, which in the ion are structurally equivalent. There is no such equilibration, as was shown in Part I. Hence the second stage (*b*) must be faster than the possible reverse step of stage (*a*), and the intermediate (I) decomposes as soon as it is formed.



(II)



(III)



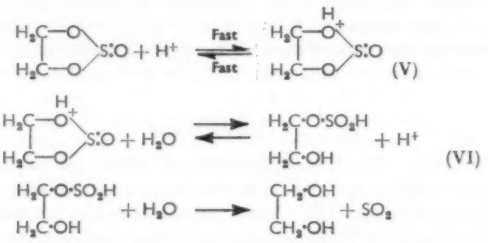
(IV)

1 : 3-Butylene sulphite reacts with alkali about a quarter as fast as does trimethylene sulphite. That the effect of such a structural change should be small is not surprising, since in all the examples studied, which include the structural types (II), (III), and (IV),

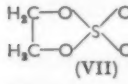
[1] Long, Pritchard, and Stafford, *J. Amer. Chem. Soc.*, 1957, **79**, 2362.

the diol recovered from the hydrolysis in enriched water was found to be isotopically normal, within experimental error. This implies that sulphur–oxygen bond-fission prevails in these cases to the extent of 95% or more, and this conclusion applies to both stages of the hydrolysis. Thus, the reaction-centre is far removed from the point of structural change.

Acid-catalysed Hydrolysis.—This also is a multi-stage reaction. The first step is a pre-equilibrium proton-transfer (Part II), and is followed by a slow displacement of sulphur dioxide. This step is bimolecular, and, as for the alkaline hydrolysis, must take place in stages; it could in principle involve the accumulation of an intermediate (VI), the conjugate acid of (I). The following is a representation of the process for the case of ethylene sulphite; there is no evidence as to the position of the proton in the intermediate (V), and this has been assigned arbitrarily.

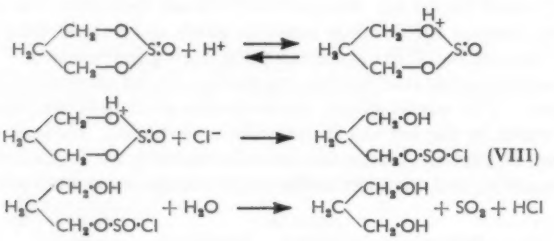


If the formation of an intermediate such as (VI) were reversible to any appreciable extent, the oxygen of the water would equilibrate with that attached to the sulphur atom. It has been shown that this is not so. Hence the intermediate (VI) must decompose to products more rapidly than it reverts to reactants.


(VII)

An alternative formulation of this intermediate is as in the structure (VII), in which water has been added to the S:O-group (cf. ref. 2). We have not distinguished between these possible intermediates, but the same arguments exclude that structure (VII) is in reversible equilibrium with the reactants.

Similar arguments apply to the reactions of kinetic form $d[SO_2]/dt = k[\text{Sulphite}][H^+][Cl^-]$. In these, the halide ion takes the place of a water molecule, and sulphur–oxygen bond-fission is still observed. The most probable reaction-sequence, formulated here for trimethylene sulphite, is as follows:



The intermediate (VIII) is also an intermediate in the reaction between a 1 : 3-diol and thionyl chloride. This reaction gives a mixture of 1 : 3-sulphite [route (*c*)] and chlorohydrin [route (*d*)] in similar proportions. Preparatively, under quite a variety of conditions of reaction, path (*d*) (to chlorohydrin) is always followed to a very considerable extent; it

[2] Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626.

is very difficult to increase the yield of 1 : 3-sulphite in this condensation to greater than about 30%.[3] No chlorohydrin is produced *via* intermediate (VIII) [and therefore path (*d*)], in the halide-catalysed hydrolysis of trimethylene sulphite; it is presumed, therefore, that path (*c*) is also not followed, and the intermediate (VIII) is hydrolysed as fast as it is formed.

Structural Effects.—Alkaline hydrolysis. The greater reactivity towards hydroxide ion of the 1 : 2- than of the 1 : 3-cyclic sulphites is qualitatively similar to the behaviour of analogous phosphates;[4] ethylene hydrogen phosphate is hydrolysed by alkalis *ca.* 10^6 times more rapidly than trimethylene or dimethyl hydrogen phosphate. It has been suggested that this very high reactivity of ethylene hydrogen phosphate results from internal repulsions between the lone-pair electrons of the oxygen atoms. A similar explanation could perhaps be applied to cyclic sulphites. Here, as in the phosphate series, the 1 : 3-cyclic compounds have a reactivity towards hydroxide ion which is similar to that of the dialkyl compounds,[5] and both are less reactive than the 1 : 2-compounds, but as the latter in the sulphite series are too reactive for conventional measurement we cannot yet compare the rates.

Acid hydrolysis. The rates and Arrhenius parameters of the acid hydrolyses of the 1 : 2- and 1 : 3-cyclic sulphites vary little with structural changes. The rates (relative to ethylene sulphite) are: propylene,* 1; (—)-2 : 3-butylene, 0·8; *meso*-2 : 3-butylene, 1·2; tetramethylethylene, 0·7; 3-chloropropylene*, 0·3; trimethylene, 4; 1 : 3-butylene,* 2·4. Comparison labelled* were made at 100°, the others at 35°.

The effect of substituents is small, as might be expected, because the substituent groups are well removed from the reaction centre. Changes in ring size have a small effect; in contrast with the situation in alkaline hydrolysis, the six-membered compounds are the more reactive. It is not known whether this arises from a difference in basicity of the two esters, or from a difference in the relative reactivities of their conjugate acids. Changes in ring size have little effect upon the basicities of saturated heterocyclic and carbocyclic nitrogen bases,[6] and from analogy with these we might expect the basicities of the 1 : 2- and 1 : 3-cyclic sulphites to be similar.

There is a considerable difference between the relative reactivities of sulphites and phosphates in acid and alkaline solution. The high reactivity of ethylene hydrogen phosphate (relative to the dialkyl hydrogen phosphates) appears in acid as well as alkaline hydrolysis. This is not so for the sulphites. Preliminary results show that diethyl sulphite hydrolyses faster than either 1 : 2- or 1 : 3-cyclic sulphites in acid solution. These different reactivity-sequences are not due to a different charge-type of reaction, because the relative rates of acid hydrolysis are similar in the presence and absence of halide ions, which specifically catalyse the reaction by attacking the sulphur atom.

We are indebted to Miss P. Yalden for technical assistance.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER STREET, LONDON, W.C.1. [*Received, July 30th*, 1958.]

[3] Rovira and Halasz, *Compt. rend.*, 1941, **212**, 644.
[4] Westheimer, Chem. Soc. Spec. Publ., 1958, No. 8, 1.
[5] Voss and Blanke, *Annalen*, 1931, **485**, 258.
[6] Brown, McDaniel, and Häflinger in "Determination of Organic Structure by Physical Methods," Ed. Braude and Nachod, Academic Press, New York, 1955.

XUM

961. *Nucleophilic Displacements in Organic Sulphites. Part IV.* The Effects of Added Salts on the Solubility of Ethylene Sulphite.*

By E. D. Davies and J. G. Tillett.

Added salts have marked specific effects on the rate of acid-catalysed hydrolysis of ethylene sulphite. Since interpretation of these data involves consideration of the activity coefficients of initial and transition states for the reaction, the corresponding effects on the activity coefficient of ethylene sulphite have been estimated by determining its solubility at 25° in aqueous solutions of various uni-univalent electrolytes.

Experimental.—Ethylene sulphite had b. p. 88°/52 mm., n_D^{25} 1·4450. The salts used were either " AnalaR " or were recrystallised and dried. Tetraethylammonium perchlorate was prepared from the corresponding hydroxide.

Excess of ethylene sulphite was added to a known volume of salt solution. The mixture was placed in a thermostat for 1 hr. and vigorously stirred. It was then allowed to settle; portions (5 ml.) of the aqueous layer were removed and titrated with 0·905M-sodium hydroxide, thymolphthalein being used as indicator. The results are given in the Table:

Salt	[Salt] (M)	NaOH (ml.)	$S_i°/S_i$	log $S_i°/S_i$	K
None	—	17·80	—	—	—
NaCl	1·0	14·50	1·228	0·0890	0·089
NaCl	2·0	12·15	1·465	0·1659	0·083
NaCl	3·0	10·00	1·780	0·2504	0·081
NaBr	1·0	16·40	1·085	0·0356	0·0356
NaBr	2·0	15·30	1·163	0·0657	0·0329
$NaClO_4$	2·0	46·11	0·3860	−0·4134	−0·207
$NaO·SO_2·C_7H_7$	1·0	32·07	0·5550	−0·2556	−0·256
Et_4NClO_4	0·1	17·91	0·9940	−0·0026	−0·026
KI	1·0	19·84	0·8973	−0·0471	−0·047
Et_4NCl	1·0	20·53	0·8670	−0·0620	−0·062
KCl	1·0	15·66	1·137	0·0557	0·056

The solubility of ethylene sulphite was 18·0 g./100 ml. The effect of added salts on the activity coefficient of a non-electrolyte is given [1] by the equations:

$$\log f_i/f_i° = \log S_i°/S_i = k_s c_s + k_i(S_i - S_i°)$$

Here $f_i°$ and f_i are the activity coefficients in the pure solvent and in the solvent with added salt; $S_i°$ and S_i are the corresponding solubilities; c_s is the concentration of the salt; k_s is the salting-out parameter, *i.e.*, the parameter which takes into account interaction between ions and non-electrolytes; and k_i is the self-interaction parameter.

If $S_i°$ and S_i are low, the last term may be neglected and the following relationship holds:

$$\log f_i/f_i° = \log S_i°/S_i = k_s c_s$$

In the present case this assumption cannot be made, but the Setchenow equation, which is of similar form, would be expected to hold, *viz.*:

$$\log S_i°/S_i = K c_s$$

where K is the Setchenow constant. Values of K are calculated from the results and indicated in the table.

The results show that sodium chloride, sodium bromide, and potassium chloride decrease the solubility of ethylene sulphite in water, *i.e.*, they salt-out this ester. Sodium perchlorate, sodium toluene-*p*-sulphonate, potassium iodide, and tetraethylammonium chloride have the opposite effect, whereas tetraethylammonium perchlorate has hardly any effect.

* Parts I—III, preceding papers.

[1] Long and McDevitt, *Chem. Rev.*, 1952, **51**, 119.

XUM

The salting-in of ethylene sulphite by perchlorate ions is in accord with the observed salting in by perchlorate ions of ethyl acetate,[2] ethyl methyl ketone,[3] and γ-butyrolactone.[4]

The salting in by the tetraethylammonium chloride is to be expected because of the large size of the cation, but the negligible effect of the corresponding perchlorate is unexpected.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER ST., LONDON, W.C.1. [*Received, July 30th*, 1958.]

[2] Waind, *J.*, 1954, 2879.
[3] Duclaux and Derand-Gasselin, *J. Chim. phys.*, 1938, **35**, 189.
[4] Long, McDevitt, and Dunkle, *J. Phys. Colloid Chem.*, 1951, **55**, 814.

---

962. *A Rapid Method for the Calculation of the Molecular-orbital Secular Equation.*

By D. S. URCH.

MANY applications of molecular-orbital theory require the construction of a determinant whose roots give the first approximation to the energy levels of the system under consideration. For large molecules and molecules including hetero-atoms this is difficult and tedious. The following simple direct method for the calculation of the secular equation has therefore been devised. Its extension to include variable parameters is simple and is also described.

(I)

Definition of Symbols.—Common symbols have their usual meaning.[1] If r is a hetero-atom and s is a carbon atom, then let

$$x = (H_{rr} - ES_{rr})/H_{rs} = (\alpha_c - E)/\beta$$
$$h.\beta = (H_{rr})_{\text{hetero-atom}} - (H_{rr})_{\text{carbon atom}}; \quad k.\beta = H_{rs}$$

Consider the system (I) which is a portion of any given molecular orbital of energy x, with coefficients a_r at the rth atom. This system can be considered as an isolated system about a_1 since atom 1 is assumed to interact only with its immediate neighbours, $a_{2,3,\&4}$. It is then possible to write

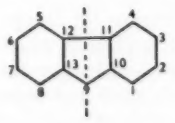
$$a_2 + a_3 + a_4 + a_1.x = 0 \qquad . \; . \; . \; . \; . \; . \; . \; . \; (1)$$

by using the normal simplifications.[2] It is more convenient if x, as used in this paper, has the value normally ascribed to $-x$. Thus for the roots of the final equation positive values of x are bonding (normally negative roots) and negative values are anti-bonding (normally positive roots).

Thus
$$\sum_{+\neq 1} a_r = a_1.x \text{ (r adjacent to 1)} \qquad . \; . \; . \; . \; . \; . \; . \; (2)$$

Equation (1) has the same array of coefficients as would occur in the corresponding line in the secular determinant.

It is possible to write equations of the same form as (1) or (2) about every atom in the molecule. Thus all the coefficients can be evaluated in terms of a few. As there are n atoms in the molecule there will be n equations so that finally all the coefficients can be eliminated leaving an equation in x alone. This is the same equation as would have been obtained by the solution of the secular determinant [(eqn. (3)].



(II)

Variable parameters (*e.g.*, about a hetero-atom) are best considered about the last atom in order that over-complicated expressions be not carried from atom to atom.

Fluorenyl System.—As an example, consider the fluorenyl system (I). The simplifying effect of symmetry is used whenever possible. The broken line is the axis of symmetry.

[1] Coulson, "Valence," Oxford Univ. Press, 1952, p. 60.
[2] Huckel, *Z. Physik*, 1931, **70**, 204, 227.

XUM

Anti-symmetric levels. These are the same as the anti-symmetric levels of diphenyl.

Symmetric levels. *A.* For a homo-atomic system:

Let $$a_2 = a_7 = m; \quad a_3 = a_6 = n$$

Now apply eqn. (2) successively around the molecule:

About atom 3 (or 6) $a_2 + a_4 = a_3.x \;\; \therefore a_4 = n.x - m = a_5$

About atom 2 (or 7) $a_1 + a_3 = a_2.x \;\; \therefore a_1 = m.x - n = a_8$

About atom 4 (or 5) $a_3 + a_{11} = a_4.x \;\; \therefore a_{11} = n(x^2 - 1) - m.x = a_{10}$

About atom 1 (or 8) $a_2 + a_{10} = a_1.x \;\; \therefore a_{12} = m(x^2 - 1) - n.x = a_{13}$

About atom 11 (or 12) $a_4 + a_{12} + a_{10} = a_{11}.x$

$$\therefore (nx - m) + n(x^2 - 1) - mx + m(x^2 - 1) - nx = x[n(x^2 - 1) - mx]$$

$$\therefore m = \frac{(x - 1)(x^2 - 1)}{2(x^2 - 1) - x}.n = kn$$

About atom 10 (or 13) $a_9 + a_{11} + a_1 = a_{10}.x$

$$\therefore a_9 = m.x(x^2 - 1) - n.x^2 - n(x^2 - 1) + m.x - m.x + n$$

$$\therefore a_9 = (x^2 - 1)(m.x - 2n)$$

About atom 9 $a_{13} + a_{11} = a_9.x \;\; \therefore a_9 = 2[m(x^2 - 1) - n.x]/x$

thus $(x^2 - 1)(m.x - 2n) = 2[m(x^2 - 1) - n.x]/x$

or $(x^2 - 1)(k'.x - 2n) = 2[k'(x^2 - 1) - x]/x$

Hence $$x(x^2 - 1).(k'.x - 2n) - 2[k'(x^2 - 1) - x] = 0 \quad . \quad . \quad . \quad . \quad (3)$$

$$\text{when } k' = \frac{(x - 1).(x^2 - 1)}{2(x^2 - 1) - x}$$

B. For a hetero-atomic system: Let atom 9 be the hertero-atom. The parameters h and k can now be included (others for the inductive effect on neighbouring atoms could be added if desired).

Equations are evaluated as before but about atoms 9, 10, and 13 the parameters must be included. Thus, about atom 10 (or 13)

$$a_9.k + a_{11} + a_1 = a_{12}.x \;\; \therefore a_9.k = (x^2 - 1).(m.x - 2n)$$

about atom 9 $$k.(a_{13} + a_{10}) = a_9.(x - h)$$

$$\therefore a_9k = k^2.2[m(x^2 - 1) - nx]/(x - h)$$

$$\therefore \frac{k^2}{(x - h)} = \frac{(x^2 - 1)(k'x - 2)}{2[k'(x^2 - 1) - x]} \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The above equations have been arrayed in a formal manner. In practice it is possible to step round a molecule very quickly and write the coefficients beside the diagram. This method is very much easier and quicker than the construction and solution of the determinant and enables coefficients to be found directly for any orbital at any atom with no extra labour.

The inclusion of continuously variable parameters instead of guessed digits for hetero-atomic factors enables the variation of energy levels to be observed as in (II), in which various fixed values have been given to h and the effect of the variation of k upon the energy levels of the π electrons over the whole molecules has been found in each case from eqn. (4).

The author thanks Professor Dewar for his invaluable help and the D.S.I.R. for a maintenance grant.

Queen Mary College, Mile End Road, London, E.1.
[*Present Address.*—Sterling Chemical Laboratory,
Yale University, New Haven, Connecticut.]

[*Received, February 21st,* 1958.]

963. *Characterisation of Thiols by Means of their* p-p′-*Nitrophenylazobenzoyl Derivatives.*

By El S. Amin.

p-p′-Nitrophenylazobenzoyl chloride, already used for identification and separation of alcohols [1] and amines,[2] has now been applied for those purposes to thiols. The chloride with nine thiols has given the thiol-esters in fairly good yields on reaction in pyridine–benzene at convenient temperatures. The esters have sharp melting points in a convenient range, in contrast to other reagents,[3] and crystallise well. Occasionally contaminating nitrophenylazobenzoic acid requires chromatographic removal. The esters are brightly coloured, which assists in chromatographic separations, some examples of which are recorded below. The technique has been used to confirm [4] the presence of methanethiol in the Egyptian radish.

Experimental.—Evaporations were effected under reduced pressure at 50°. M. p.s were determined on a Kofler microscope stage.

Preparation of the thiol-esters. The thiol (0·5 mmole) and *p-p′*-nitrophenylazobenzoyl chloride [1] (0·725 mmole) were kept in 1 : 1 pyridine–benzene (30 ml.) at 5°, room temperature, or 50° (according to the b. p. of the thiol) for 1—2 days. The mixture was then treated with water and extracted with 1 : 1 benzene–ether (50 ml.). The extract was washed with 20% sulphuric acid, filtered, washed with water, aqueous sodium carbonate, and water, concentrated to *ca.* 20 ml., and filtered through activated alumina. The main, lower red band was eluted with benzene, and the product recrystallised from ethanol or acetone (as needles). The p-p′-*nitrophenylazo*(*thiolbenzoates*) shown in the Table were thus prepared in 80—85% yield.

Hydrolysis by potassium hydroxide (1 mol.) in 2-methoxyethanol for a few hr. at room temperature or 1—2 days at 5° regenerated the thiol

Thiol-esters, $NO_2 \cdot C_6H_4 \cdot N_2 \cdot C_6H_4 \cdot CO \cdot SR$

R	Colour	Solvent	M. p.	Found N (%)	Formula	Reqd. N (%)
Me	Red	Ethanol	162°	14·0	$C_{14}H_{11}O_3N_3S$	14·0
Et	Red	EtOH	154	13·2	$C_{15}H_{13}O_3N_3S$	13·3
Pr^n	Orange	EtOH	146	12·9	$C_{16}H_{15}O_3N_3S$	12·8
Bu^n	,,	EtOH	134	12·5	$C_{17}H_{17}O_3N_3S$	12·7
n-C_5H_{11}	,,	$COMe_2$	130	11·6	$C_{18}H_{19}O_3N_3S$	11·8
n-C_6H_{13}	,,	EtOH	124	11·1	$C_{19}H_{21}O_3N_3S$	11·1
n-C_7H_{15}	,,	$COMe_2$	125	11·2	$C_{20}H_{23}O_3N_3S$	11·0
n-C_9H_{19}	Orange-yellow	EtOH	125	10·3	$C_{22}H_{27}O_3N_3S$	10·0
Ph	Orange	EtOH	224	11·3	$C_{19}H_{13}O_3N_3S$	11·8
p-C_6H_4Me	,,	EtOH	172	11·5	$C_{20}H_{15}O_3N_3S$	11·1
CH_2Ph	,,	EtOH	169	11·0	$C_{20}H_{15}O_3N_3S$	11·1

Chromatography. The two layers formed by a 15 : 1 : 3 v/v mixture of decane, nitromethane, and dimethylformamide were separated. A tube (*ca.* 40 cm. long, 2 cm. in diameter) was half-filled with the decane layer. A 1 : 1 w/w mixture (40 g.) of the other layer and kieselguhr (dried at 110°) was made into a sludge with the decane layer (40 c.c.) and added to the column. When the column had drained, the thiol-ester (15 mg.) in the decane layer was added and the chromatogram was developed with the decane layer under slight suction. Materials eluted were recrystallised from ethanol. The following results are typical.

(i) A mixture of the esters (1 mg. each) from methane-, propane-1-, pentane-1-, and nonane-1-thiol was chromatographed on a 10 × 2 cm. column. Eluent fractions were 1 c.c. each. Fractions 1—10 yielded nonyl ester (0·6 mg.), fractions 11—23 pentyl ester (0·7 mg.), fractions 24—50 propyl ester (0·5 mg.), and fractions 55—80 methyl ester (0·7 mg.), all identified by m. p. and mixed m. p.

(ii) A mixture of the esters (1 mg. each) from ethane-, propane-1-, butane-1-, pentane-1-, and

[1] Hecker, *Chem. Ber.*, 1955, **88**, 1666; Amin and Hecker, *ibid.*, 1956, **89**, 695.
[2] Amin, *J.*, 1957, 3764.
[3] Bost, Turner, and Norton, *J. Amer. Chem. Soc.*, 1932, **54**, 1985; Wertheim, *ibid.*, 1929, **51**, 3661.
[4] Nakamura, *Biochem. Z.*, 1925, **164**, 31.

XUM

hexane-1-thiol were chromatographed on kieselguhr impregnated with dimethyloxosilane,[2] the solvents being 5 : 5 : 3-v/v formamide–nitromethane–nonane, in a 11·8 × 2 cm. column. Eluent fractions were: nos. 1—10, 3 ml.; nos. 11—25, 4 ml.; nos. 26—31, 5 ml. each. Photometric readings showed slight overlap for the pairs ethyl–propyl, propyl–butyl, and butyl–pentyl, but a gap of 6 fractions (4 ml. each) between the pentyl and the hexyl ester.

Examination of Strophanum sativum Egyptiacum. Radish roots (5 kg.) were crushed with pure sand at 0° and extracted with light petroleum (b. p. 30—50°) at 5°. The petroleum extract (5 l.) was dried (Na_2SO_4), mixed with dry benzene (5 l.), *p-p'*-nitrophenylazobenzoyl chloride (0·5 g.), and pyridine (10 ml.), and was kept at 5° for a week. The solution was then warmed in a closed vessel at 30—60° for 6 hr., concentrated to 250 ml., washed with 20% sulphuric acid, filtered, washed in turn with water, sodium carbonate solution, and water, and placed on an alumina column. Of the two coloured bands produced the lower was eluted with benzene, giving 50·4 mg. of material which on hydrolysis gave the odour of methanethiol. The upper band on elution (5·8 mg.) and hydrolysis gave no foul smell.

The substance from the lower band (40 mg.) was subjected to partition chromatography on kieselguhr–dimethyloxosilane with formamide–nitromethane–nonane, giving two bands. Elution of the main lower band and recrystallisation from ethyl alcohol gave red needles (26 mg.), m. p. 162° alone or mixed with the methyl thiol ester (Found: N, 14·0%).

FACULTY OF SCIENCE,
ALEXANDRIA UNIVERSITY, EGYPT.

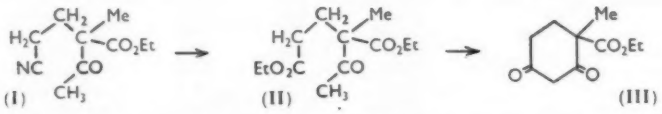
[*Received, May 5th,* 1958.]

---

964. *Preparation of Ethyl* 1-*Methyl*-2 : 4-*dioxo*cyclo*hexane*-1-*carboxylate.*

By S. M. MUKHERJI, R. K. SHARMA, and O. P. VIG.

ETHYL 1-METHYL-2 : 4-DIOXO*cyclo*HEXANE-1-CARBOXYLATE (III), first prepared 20 years ago,[1] has been prepared by us by a more convenient method as an intermediate in a projected synthesis of artificial steroid gonadogens and we now record it in view of the recent publication of Stetter and Milbers[2] on analogous *cyclo*hexanediones. Ethyl methyl-



acetoacetate[3] with acrylonitrile[4] and 30% methanolic potassium hydroxide in *tert.*-butyl alcohol gave the nitrile ester (I) which on alcoholysis[5] gave a 79% yield of diethyl α-methyl-α-acetylglutarate (II). Alcohol-free potassium *tert.*-butoxide cyclised this in 70·4% yield to the monoester (III).

Experimental.—Ethyl α-methyl-α-2-cyanoethylacetoacetate (I). To ethyl methylacetoacetate[3] (160 g.) and 30% methanolic potassium hydroxide (9 c.c.) in *tert.*-butyl alcohol (300 c.c.) was added acrylonitrile (90 g.) dropwise with stirring at 30—35°. The solution was then neutralised and worked up in the usual manner. The *ester* (I) was obtained at 142—146°/5 mm. (yield 145 g., 66·2%) (Found: C, 60·9; H, 7·4. $C_{10}H_{15}O_3N$ requires C, 60·9; H, 7·7%).

Diethyl α-methyl-α-acetylglutarate (II). A solution of ethyl α-methyl-α-2-cyanoethylacetoacetate (II) (145 g.) in absolute alcohol (300 c.c.) was saturated with dry hydrogen chloride in 8 hr. The temperature was kept below 0° and the contents were continuously and efficiently stirred throughout and later set aside overnight. After removal of most of hydrogen chloride at 40° at the water-pump the contents were poured into an excess of ice-cold 20% sodium carbonate solution in a thin stream and at once extracted with ether (3 × 300 c.c.). The

[1] Lin and Robinson, *J.*, 1938, 2006.
[2] Stetter and Milbers, *Chem. Ber.*, 1958, **91**, 374.
[3] Folkers and Adkins, *J. Amer. Chem. Soc.*, 1931, **53**, 1416.
[4] Misra and Shukla, *J. Indian Chem. Soc.*, 1952, **29**, 201.
[5] Kimbal, Jefferson, and Pikes, *Org. Synth.*, Coll. Vol. II, 1946, p. 284.

ether extract was washed free from alcohol with ice-cold 5% sodium chloride solution and then shaken with ice-cold 10% sulphuric acid solution (300 c.c.). This was repeated twice and the acid layer containing the imidate was separated and heated at 50° for ½ hr. in order to hydrolyse it. It was cooled and extracted with ether. The acid solution was again heated at 80—90° and extracted with ether. All the ether extracts were combined, washed first with sodium carbonate solution, then with water, and dried (Na_2SO_4). After removal of the ether the residue was fractionated, giving the diester (II), b. p. 132—134°/5 mm. (142 g., 79·1%) (Found: C, 59·4; H, 8·4. $C_{13}H_{20}O_5$ requires C, 59·0; H, 8·25%).

Ethyl 1-*methyl*-2 : 4-*dioxocyclohexane*-1-*carboxylate* (III). The diester (II) (70 g.) in dry ether (200 c.c.) was added dropwise with swirling to a suspension of alcohol-free potassium *tert.*-butoxide (from 12·5 g. of potassium) in dry ether (500 c.c.). The mixture which soon solidified was refluxed for 3 hr. and cooled, and 3% sodium hydroxide solution (200 c.c.) was added. The aqueous layer after being extracted with ether (2 × 100 c.c.) was acidified with dilute hydrochloric acid and the separated oil extracted with ether. This ether extract was washed with water, dried, and evaporated. The diketo-ester (III) obtained had b. p. 145—148°/5 mm., m. p. 85° (from benzene) lit.,[1] m. p. 81·5—82·5° (40 g., 70·4%) (Found: C, 61·0; H, 6·9. Calc. for $C_{10}H_{14}O_4$: C, 60·6; H, 7·1%).

CHEMISTRY DEPARTMENT, PANJAB UNIVERSITY,
HOSHIARPUT, INDIA.

[*Received, May 19th*, 1958.]

---

965. *Reactions of Disodium Pentacyanoamminoferrate with Aromatic Amines. Part III.*[1] *The Preparation of* 2 : 7-*Dimethylphenazine from* p-*Toluidine.*

By E. F. G. HERINGTON.

THE reaction of disodium pentacyanoamminoferrate $Na_2[Fe(CN)_5NH_3]$ with many aromatic amines gives highly coloured solutions [1-3] containing ions of the general structure $[Fe(CN)_5NHR]^{3-}$ which are stable, but reaction of excess of the salt with *p*-toluidine gives a complex which decomposes and deposits a brown solid from the solution. A sample of 2 : 7-dimethylphenazine has been separated by chromatography from this crude product in a yield of 40% of the weight of *p*-toluidine taken.

Bamberger and Ham [4] obtained the heterocyclic base by reaction of *p*-nitrosotoluene with concentrated sulphuric acid. Their observation that 2 : 7-dimethylphenazine is not formed by the action of *p*-toluidine on *p*-nitrotoluene in the presence of sodium hydroxide although phenazine is formed by the action of aniline on nitrobenzene under similar conditions has been confirmed in the present study.

The following compounds may be mentioned as some of the products identified when *p*-toluidine in aqueous solution is oxidized by various reagents: *p*-azotoluene, 4 : 4'-dimethylazobenzene, 4-amino-2 : 5-toluquinone di-*p*-tolylimine, 4-*p*-toluidino-2 : 5-toluquinone di-*p*-tolylimine, 2 : 7-dimethyl-3-*p*-toluidinophenazine, and di-*p*-tolylamine.

However, direct oxidation of *p*-toluidine to 2 : 7-dimethylphenazine has only been reported to take place photochemically,[5] so the action of disodium pentacyanoamminoferrate appears to be unique.

The mechanism of the formation of 2 : 7-dimethylphenazine by the reaction of disodium pentacyanoamminoferrate with *p*-toluidine is probably as follows. The first step is the replacement of ammonia by *p*-toluidine [equation (1)] and this is then followed by the reaction shown in equation (2).

$$Na_2[Fe(CN)_5NH_3] + H_2N{\cdot}C_6H_4Me = Na_2[Fe(CN)_5H_2N{\cdot}C_6H_4Me] + NH_3 \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$Na_2[Fe(CN)_5H_2N{\cdot}C_6H_4Me] + NaOH = Na_3[Fe(CN)_5HN{\cdot}C_6H_4Me] + H_2O \quad . \quad . \quad . \quad . \quad . \quad (2)$$

[1] Part II, Herington, *J.*, 1958, 4683.
[2] Herington, *Nature*, 1955, **176**, 80.
[3] Herington, *J.*, 1956, 2747.
[4] Bamberger and Ham, *Annalen*, 1911, **382**, 82.
[5] Malaviya and Dutt, *Proc. Acad. Sci. United Provinces Agra Oudh, India*, 1935, **4**, 319; *Chem. Abs.*, 1936, **30**, 1056.

XUM

The resulting pentacyanoferrate complex is unstable, and as a result two of the complex radicals shown in equation (2) react to yield 2-amino-5 : 4′-dimethyldiphenylamine; for a discussion of the similar instability of the ion $[Fe(CN)_5HN{\cdot}C_6H_5]^{3-}$ see Part II.[1] The 2-amino-5 : 4′-dimethyldiphenylamine then reacts to give the ion $[Fe(CN)_5,NH{\cdot}C_6H_3Me{\cdot}HN{\cdot}C_6H_4Me]^{3-}$ which is oxidized further to close the central ring and to yield 2 : 7-dimethylphenazine.

Support for this mechanism was obtained when it was shown that disodium pentacyanoamminoferrate reacts with 2-amino-5 : 4′-dimethyldiphenylamine to give material containing 2 : 7-dimethylphenazine. Ring closure occurred in this reaction at room temperature, whereas hitherto it had been necessary to heat *o*-aminodiphenylamines with litharge to a very high temperature in order to obtain phenazines.[6]

Experimental.—Oxidation of p-*toluidine.* A solution of disodium pentacyanoamminoferrate[3] (2·5 g.), in 0·025N-sodium hydroxide (70 ml.), was poured on finely pulverized *p*-toluidine (0·25 g.), and the mixture was shaken for 7 days. The solid (0·16 g.) was then removed from the muddy green solution, washed with water, and dried in a vacuum over calcium chloride It gave a strong green colour with concentrated sulphuric acid in the cold, and a red solution when heated.

The solid in benzene (20 ml.) was passed through activated alumina (20 × 1·8 cm.). Washing with benzene removed successively a diffuse band (fraction 1), a yellow band (fraction 2), and a light brown band (fraction 3). Other fractions were washed out but were not examined.

4 : 4′-*Dimethylazobenzene.* The solid (0·002 g.) in fraction 1 had m. p. 140° and gave a yellow colour with concentrated sulphuric acid in the cold. It was shown to be 4 : 4′-dimethylazobenzene by a comparison of its infrared spectrum with that of a sample prepared by the reaction between *p*-nitrosotoluene and *p*-toluidine.

2 : 7-*Dimethylphenazine.* Fraction 3 from the crude product was rechromatographed on activated alumina. The yellow solution obtained was combined with fraction 2 and after removal of the benzene yielded 0·1 g. of solid [Found: C, 80·5; H, 6·4; N, 13·2%; *M* (Rast), 215. Calc. for $C_{14}H_{12}N_2$: C, 80·8; H, 5·8; N, 13·5%; *M*, 208]. This dissolved in concentrated sulphuric acid to give a strong red colour which yielded a bright yellow solution on dilution with water (characteristic of phenazine derivatives). It had m. p. 162° alone or mixed with 2 : 7-dimethylphenazine (m. p. 163°) prepared from *p*-nitrosotoluene, and the infrared spectra of these materials were identical.

p-Tolylhydroxylamine was prepared according to the second method described by Bamberger and Rising.[7] *p*-Nitrosotoluene (3·8 g.), made therefrom,[8] was introduced in glacial acetic acid (12 ml.) into ice-cold concentrated sulphuric acid (12 ml.) with stirring. After ½ hr. the product was poured on ice (50 g.) and water (50 g.). Bamberger and Ham [4] reported that the product obtained from this reaction was complex and contained at least six components which were difficult to separate. In the present experiments 2 : 7-dimethylphenazine *N*-oxide was isolated from the crude product by chromatography. The acid aqueous solution was filtered and extracted with benzene and the extract was passed through activated alumina (16 × 1·8 cm.). The chromatogram was developed with benzene and the first (yellow) and the second (orange) fraction (purplish on the column) were rejected. The third (yellow-orange) fraction contained slightly impure 2 : 7-dimethylphenazine *N*-oxide, m. p. 199° (lit.,[4] m. p. 204—205°). The oxide (0·1 g.) was treated in concentrated hydrochloric acid with a concentrated hydrochloric acid solution of stannous chloride. The green precipitate [4] was filtered off and boiled with 20% sodium hydroxide solution, and the resulting 2 : 7-dimethylphenazine was removed; it had m. p. 163° (Bamberger and Ham give m. p. 163°).

The chromatogram showed at least 9 other bands, indicating the complexity of the material.

2-*Amino*-5 : 4′-*dimethyldiphenylamine.* 4 : 4′-Dimethylhydrazobenzene [9] was isomerized to 2-amino-5 : 4′-dimethyldiphenylamine by the action of hydrochloric acid as reported by Täuber.[10]

[6] Campbell, Le Fèvre, Le Fèvre, and Turner, *J.*, 1938, 404; Mikhailov and Blokhina, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1950, 304; *Chem. Abs.*, 1950, **44**, 9452.

[7] Bamberger and Rising, *Annalen*, 1901, **316**, 280.

[8] Wieland and Roseeu, *Ber.*, 1915, **48**, 1117.

[9] Cf. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., London, 1941, p. 320.

[10] Täuber, *Ber.*, 1892, **25**, 1019.

XUM

Oxidation of 2-amino-5 : 4′-dimethyldiphenylamine by $Na_2[Fe(CN)_5NH_3]$ *and separation of the products.* The conditions were those described for the reaction of *p*-toluidine with $Na_2[Fe(CN)_5NH_3]$. The solid obtained was passed in benzene through alumina. The pink material in the first band was rejected, but the yellow solution which followed yielded 0·04 g. of solid (16% of the wt. of amine), m. p. 162° not depressed when mixed with 2 : 7-dimethylphenazine prepared from *p*-nitrosotoluene. The infrared spectra of these two specimens were identical.

A preliminary note on this work has been published.[2] The work described formed part of the research programme of the Chemical Research Laboratory and this note is published by permission of the Director.

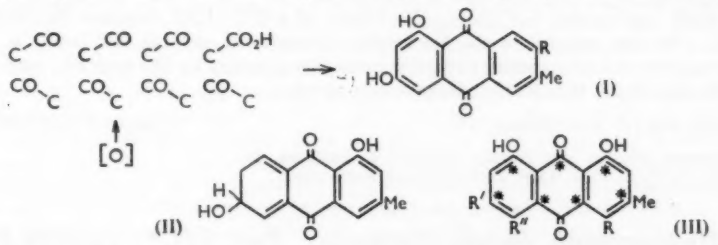
NATIONAL CHEMICAL LABORATORY,
TEDDINGTON, MIDDLESEX.

[*Received, June 16th*, 1958.]

966. *Studies in Relation to Biosynthesis. Part XIX.* The Biosynthesis of Helminthosporin.*

By A. J. BIRCH, A. J. RYAN, and HERCHEL SMITH.

IN 1953 it was suggested[1] that the structures of a large group of anthraquinones were consistent with a phytochemical synthesis by a process involving head-to-tail linkage of acetic acid units and appropriate cyclisation and secondary reactions. The example most closely related to this scheme is the anthraquinone acid, endocrocin (I; R = CO_2H), from *Nephromopsis endocrocea*[2] and *A. amstelodami*,[3] which would be formed from eight acid units with the introduction of one quinone-oxygen atom. Apart from decarboxylated analogues, *e.g.*, emodin (I; R = H), many variants of the same anthraquinone skeleton are known which are characterised by absence of oxygen substituents in the "expected" positions or possessing "additional" oxygen substituents, or both. These can be rationalised on the basis of oxidations, reductions, and dehydrations which are either known to occur in vital systems or have laboratory or biological analogies (for a discussion see ref. 4).



Originally it was our intention to study, by feeding experiments with $CH_3{\cdot}^{14}CO_2H$, the biosynthesis of flavoskyrin[5] (II) in *P. islandicum* Sopp. This substance is readily transformed by acid into chrysophanic acid (III; R = R′ = R″ = H) which is known to form a tetranitro-derivative suitable for scission by the bromopicrin method either directly or after conversion into 3-hydroxy-2 : 4 : 6-trinitrobenzoic acid.[6] We were, however, unable to obtain a culture of this organism and therefore turned to similar studies with *H. graminium* Rabenhorst. Although this organism is reported[7] to give abundant yields

* Part XVIII, *J.*, 1958, 4582.

[1] Birch and Donovan, *Austral. J. Chem.*, 1953, **6**, 360.
[2] Asahina and Fusikawa, *Ber.*, 1935, **68**, 1558.
[3] Ashley, Raistrick, and Richards, *Biochem. J.*, 1939, **33**, 1291, and references there cited; Shibata and Natori, *Pharm. Bull.* (*Japan*), 1953, **1**, 160.
[4] Birch, *Fortschr. Chem. org. Naturstoffe*, 1957, **16**, 186.
[5] Howard and Raistrick, *Biochem. J.*, 1955, **59**, 475.
[6] Léger, *Compt. rend.*, 1912, **154**, 281; *J. Pharm. Chim.*, 1912, **5**, 281.
[7] Charles, Raistrick, Robinson, and Todd, *Biochem. J.*, 1933, **27**, 499.

XUM

of helminthosporin (III; R = R′ = H, R″ = OH) and catenarin (III; R = R″ = H, R′ = OH), in our hands it gave a complex mixture of pigments from which we obtained a small quantity of helminthosporin as the only recognisable product. Owing to the lack of material the only degradation we were able to carry out on the labelled helminthosporin from $CH_3{\cdot}^{14}CO_2H$ was Kuhn–Roth oxidation. Examination of the resultant acetic acid by pyrolysis of the lithium salt [8] showed that all the radioactivity was located on the carboxyl group and that this constituted one-seventh of the activity of the labelled helminthosporin. This result is in accord with the distribution of activity (III; labelled atoms *) postulated on the basis of the suggested biosynthesis. Taken in conjunction with earlier work showing the biosynthesis of a number of mould and plant [9] products through head-to-tail linkage of acetic acid units, it provides strong presumptive evidence that a large number of anthraquinones are formed in Nature by a similar process.

Experimental.—General directions are as for Part XVII.[9]

[^{14}C]*Helminthosporin. H. graminium* Rabenhorst was grown as described earlier. After 28 days $CH_3{\cdot}^{14}CO_2Na$ (0·3 mc) in water was added to the culture medium. After a further 21 days the cultures were harvested. The dried mycelium was exhausted by percolation with chloroform, and the resulting bright red solid (16 g. from 18 l. of medium) was de-fatted with boiling light petroleum (b. p. 40—60°). The residue (12 g.) was dissolved in ethyl acetate had separated into fractions soluble in aqueous sodium hydrogen carbonate, sodium carbonate, and sodium hydroxide, denoted A, B, and C respectively. Fraction A was a red solid (0·25 g.) whicn was not examined further. Fraction B was expected to contain catenarin; it was treated with acetic anhydride in pyridine, and the product chromatographed in ether on Florisil, but no recognisable product was obtained. Fraction C (1·2 g.) had m. p. 190—210°. It was acetylated and chromatographed on Florisil as for fraction B. The fraction of m. p. 218—220° (lit.,[7] m. p. for helminthosporin triacetate 226—227°) was hydrolysed by 10% aqueous sodium hydroxide. The product was recrystallised from ethyl acetate, to give helminthosporin (0·118 g.; 9×10^{-5} mc), m. p. 220—221° (lit.,[7] m. p. 223—224°) (Found: r.m.a., 277×10^3). Kuhn–Roth oxidation gave acetic acid, collected as lithium acetate which was pyrolysed to $BaCO_3(Me)$ (Found: r.m.a., 0), and $BaCO_3(CO_2H)$ [Found: r.m.a.; 399×10^2; (1C, 396×10^2)].

This work was carried out during the tenure of a C.S.I.R.O. Overseas Studentship (by A. J. R.). We are grateful to the Rockefeller Foundation and the Distillers Co. Ltd. for financial support and to Imperial Chemical Industries Limited for the loan of counting equipment. We also thank Miss M. Hay for mycological work.

THE UNIVERSITY, MANCHESTER, 13. [*Received, June 20th,* 1958.]

[8] Cornforth, Hunter, and Popjak, *Biochem. J.*, 1953, **54**, 597.
[9] Part XVII, *J.*, 1958, 4576, and references there cited.

---

967. *Hydroaromatic Steroid Hormones. Part VII.** (±)-17*a*-Ethynyl-17*a*-hydroxy-D-homo-18 : 19-bisnorandrost-4-en-3-one.†

By A. J. BIRCH, G. A. HUGHES, and HERCHEL SMITH.

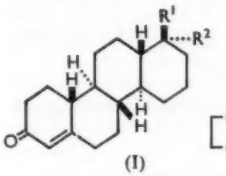
IT has been reported [1] that D-homo-18 : 19-bisnortestosterone (I; R^1 = OH, R^2 = H) is non-androgenic but possesses a high myotrophic activity. These properties are highly desirable in an anabolic agent. In Part V † we confirmed the absence of androgenic activity in the ketol (I; R^1 = OH, R^2 = H) and the propionate (I; R^1 = Et·CO_2, R^2 = H), but recent tests on the same two compounds carried out by Benger's Laboratories, Holmes Chapel, failed to substantiate the claimed myotrophic activity. As part of an attempt to determine whether any hormones based on D-homo-18 : 19-bisnorandrostane retain biological activity we have synthesised the ethynyl alcohol [I; R^1 = OH (or C:CH), R^2 = C:CH (or OH)]. The choice of this compound was due partly to the relatively low structural

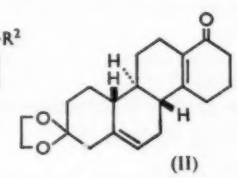
* Part VI, Birch, Pride, and Smith, *J.*, 1958, 4688.
† Nomenclature as for Part V, *J.*, 1956, 4909.
[1] Johnson, Dehn, and Chinn, *J. Org. Chem.*, 1954, **19**, 670.

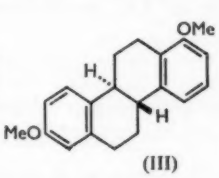
XUM

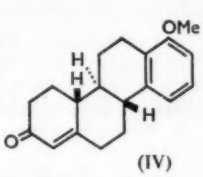
requirement for progestational activity which is apparent from the high activity of 8β-[2] and 8β : 14α-progesterone,[3] partly to the enhancement of activity in 19-norprogesterone,[4] and partly to the claim [5] that 17α-ethynyl-19-nortestosterone is a highly potent gestogen.

The synthesis of the alcohol [I; R^1 = OH (or C:CH), R^2 = C:CH (or OH)] is based on the ketone (II) obtained as an intermediate in the synthesis of the alcohol (I; R^1 = OH, R^2 = H). Reduction of this ketone with lithium in liquid ammonia gave a saturated ketone: no evidence for the formation of a less stable *cis*-isomer (cf. ref. 6) was obtained. Reaction of the latter ketone with lithium acetylide in liquid ammonia, followed by acid hydrolysis, gave the required alcohol. It has no androgenic or myotrophic activity but has not yet been tested for progestational activity. The stereochemistry at the 17*a*-position is not proved, but it is probable that the hydroxyl group has the β-configuration by analogy with the addition of alkali-metal acetylides to 17-oxo-steroids [7] and to a 9-methyl*trans*-decal-1-one. After the completion of this work, Nelson and Garland [8] reported the synthesis of what were claimed to be 18 : 19-bisnorprogesterone and 14α-hydroxy-18 : 19-bisnorprogesterone, neither of which showed progestational activity.


(I)


(II)


(III)


(IV)

During our work intermediate stages in the synthesis of the ketol (I; R^1 = OH, R^2 = H) have been re-investigated. Selective reduction of the 1 : 3 : 4-substituted benzene ring in the chrysene (III) depends, not only upon the amount of reducing agent, but also on the quality of the liquid ammonia. Reproducible yields (*ca.* 68%) of the ketone (IV) (obtained by acid-hydrolysis and base-catalysed rearrangement of the reduction product) were obtained with 30—35 atom-equiv. of lithium and with ammonia distilled from sodium.

Experimental.—(±)*17a-Ethynyl-17a-hydroxy-*D*-homo-18 : 19-bisnorandrost-4-ene-3-one* [I; R^1 = OH (or C:CH), R^2 = C:CH (or OH)]. 10-Ethylenedioxy-1 : 2 : 3 : 4 : 5 : 6 : 7 : 9 : 10 : 11 : 12 : 13 : 15β : 16α-tetradecahydro-3-oxochrysene (II) (290 mg.) in tetrahydrofuran (20 c.c.) was added dropwise with stirring to a solution of lithium (5—10 mg.) in liquid ammonia (200 c.c.; distilled from sodium), until the blue colour was discharged. Lithium (*ca.* 2 mg.) was added and the solution was decolorised by the addition of more of the tetrahydrofuran solution. The process was repeated until the liquid ammonia remained pale blue after addition of all the ketone solution. The mixture was stirred for 10 min., the blue colour was discharged with sodium nitrite, and water (100 c.c.) was added. The product was recrystallised from light petroleum (b. p. 60—80°) to give a ketone (176 mg.), m. p. 108—111°, $\nu_{max.}$ in carbon disulphide 1710, 1110, and 1050 cm.$^{-1}$. This ketone in tetrahydrofuran (30 c.c.) was added with stirring to a solution of lithium acetylide (from the metal, 250 mg.) in liquid ammonia (30 c.c.) at −70°. The mixture was stirred for 45 min. at this temperature. After 9 hr. ice-water (40 c.c.), was added, and the mixture extracted with ether–ethyl acetate (1 : 1). The product, which showed no ketonic infrared bands, was refluxed in glacial acetic acid (7·5 c.c.) and water (7·5 c.c.) for 45 min. under nitrogen. The solution was poured on a slurry of potassium hydrogen carbonate in water, and the product was collected with ether–ethyl acetate (1 : 1). It was dissolved in benzene (10 c.c.) and chloroform (2·5 c.c.) and adsorbed on Florex (Floridin Co., Warren, Pennsylvania) from which it was eluted with benzene and benzene

[2] Djerassi, Manson, and Segaloff, *J. Org. Chem.*, 1956, **21**, 490.
[3] Barber and Ehrenstein, *Annalen*, 1957, **603**, 89.
[4] Djerassi, Miramontes, and Rosenkrantz, *J. Amer. Chem. Soc.*, 1953, **75**, 4440.
[5] Hertz, Raffelt, and Tuller, *Endocrinology*, 1954, **54**, 228.
[6] Birch, Smith, and Thornton, *J.*, 1957, 1339.
[7] Cf., *e.g.*, Reichstein and Meystre, *Helv. Chim. Acta*, 1939, **22**, 728; Reichstein and Gatzi, *ibid.*, 1938, **21**, 118; and Part VI of our series.
[8] Nelson and Garland, *J. Amer. Chem. Soc.*, 1957, **79**, 6313.

XUM

containing increasing proportions of chloroform up to 50% by volume. Recrystallisation from ethanol–tetrahydrofuran gave (±)-17*a*-*ethynyl*-17*a*-*hydroxy*-D-*homo*-18 : 19-*bisnorandrost*-4-*en*-3-*one* (56 mg.), m. p. 232—235° (Found: C, 80·6; H, 8·6. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%), $\nu_{max.}$ (Nujol mull) 3360, 3280, 1670, and 1180 cm.$^{-1}$.

We are indebted to Dr. L. Golberg (Benger's Laboratories, Holmes Chapel, Cheshire) for the biological tests, and to the D.S.I.R. for a Maintenance Grant (to G. A. H.).

THE UNIVERSITY, MANCHESTER, 13. [*Received, July 14th*, 1958.]

---

968. *The Indole Alkaloids. Part II.* Vobtusine and Voacangine from* Voacanga dregei.

By B. O. G. SCHULER, A. A. VERBEEK, and F. L. WARREN.

VOBTUSINE, m. p. 286°, was first isolated by Janot and Goutarel [1] from *Voacanga afrikana* Staph. and *V. thoursii* Roem and Schultes (var. *obtusa* K. Schum); they assigned to it the formula $C_{21}H_{26}O_3N_2$ or $C_{20}H_{26}O_3N_2$. Stauffacher and Seebeck [2] recently re-isolated this alkaloid from *V. afrikana* and recorded m. p. 302—305° ± 5°.

The bark of *V. dregei* was previously extracted by Rindl and Groenewoud [3] who reported no crystalline alkaloid. We have now isolated vobtusine as the sole alkaloid of the root bark, whilst from the aerial bark it is obtained in smaller yield and mixed with larger quantities of voacangine.[4]

Vobtusine, for which we find m. p. 305—306° (decomp.), is now assigned the formula $C_{42}H_{50}O_7N_4$ on the basis of molecular-weight determinations. The double formula includes an additional 1 H_2O and avoids the use of $\frac{1}{2}H_2O$ in the formulæ for the alkaloid, the hydrochloride, $C_{42}H_{52}O_7N_4Cl_2,2C_2H_6O$, and the hydrobromide, $C_{42}H_{52}O_7N_4Br_2$. The alkaloid contains two methoxyl groups but no *C*- or *N*-methyl group. In concentrated nitric acid it dissolves to a deep blue solution. Its infrared spectrum shows bands at 1681 and 1608 cm.$^{-1}$, previously reported,[1] which are assigned to a possible amide group and a benzene nucleus respectively, and an additional band now found at 3335 cm.$^{-1}$ indicates a bonded $-NH-$ grouping. Vobtusine with selenium gives quinoline which was identified as picrate and styphnate. Under similar conditions voacangine gives 3-ethyl-5-methylpyridine (isolated as picrate) which was previously isolated on fusion of voacangine with potassium hydroxide.[5]

Despite the close association of vobtusine with voacangine in the plant, the alkaloids seemingly differ considerably in structure, and the indole double bond may not be present in vobtusine since the ultraviolet spectrum is not that of a typical indole. This double bond may be involved in the formation of the double molecule.

Experimental.—Extraction. The ground and dried aerial bark of *V. dregei* from the South Coast, Natal, was extracted with hot alcohol containing 2% of acetic acid. The extract was concentrated and poured into water. The mixture was filtered, made basic with ammonia, and extracted with chloroform. The chloroform extract was concentrated, ethanol was added, and solution was boiled until free from chloroform, filtered from the crystalline solid (vobtusine, yield 0·1%), and evaporated to dryness. The residual gum was ground with plaster of Paris, air-dried, and extracted with light petroleum. The petroleum extract gave a gum which crystallised from methanol to give voacangine (0·15% yield), m. p. 137—138°, $[\alpha]_D^{22}$ −42° (*c* 1 in chloroform) (Found: C, 71·5; H, 7·8; N, 7·6. Calc. for $C_{22}H_{28}O_3N_2$: C, 71·7; H, 7·7; N, 7·6%). Chromatography gave no other alkaloids. The root bark gave only vobtusine, in 0·5% yield.

* Part I, *J.*, 1956, 215.

[1] Janot and Goutarel, *Compt. rend.*, 1955, **240**, 1719.
[2] Stauffacher and Seebeck, *Helv. Chim. Acta*, 1958, **41**, 169.
[3] Rindl and Groenewoud, *Trans. Roy. Soc. S. Africa*, 1932, 55.
[4] Janot and Goutarel, *Compt. rend.*, 1955, **240**, 1800.
[5] *Idem, ibid.*, 1953, **237**, 1718.

XUM

Vobtusine. The solid in chloroform was added to boiling methanol and the mixture boiled until free from chloroform to give crystals of vobtusine, m. p. 305—306° (decomp.), $[\alpha]_D^{20}$ −321° (*c* 1 in chloroform) [Found: C, 69·8; H, 7·2; N, 7·6; OMe, 7·8%; *M* (ebullioscopic in $CHCl_3$), 686 ± 60. Calc. for $C_{42}H_{50}O_7N_4$: C, 69·8; H, 7·0; N, 7·8; OMe, 8·6%; *M*, 722·9].

Dry hydrogen chloride was passed into a solution of vobtusine in chloroform, and the solution evaporated to a gummy *hydrochloride* which crystallised from ethanol in prisms, m. p. 242—244° (Found: C, 62·2; H, 7·2; N, 6·0; Cl^-, 8·2. $C_{42}H_{52}O_7N_4Cl_2,2C_2H_6O$ requires C, 62·2; H, 7·2; N, 6·3; Cl, 8·0%).

One drop of hydrobromic acid was added to a suspension of vobtusine in methanol, and the mixture shaken until all the solid had dissolved. Addition of ether gave a white amorphous precipitate which crystallised slowly from acetone to give prisms of *vobtusine hydrobromide*, decomp. 290° (Found: C, 57·4; H, 6·0; N, 6·1. $C_{42}H_{52}O_7N_4Br_2$ requires C, 57·0; H, 5·9; N, 6·3%).

Vobtusine in chloroform was mixed with alcoholic picric acid, the solvent removed, the solid dissolved in alcohol, and water added. A picrate was precipitated as a heat-labile, amorphous powder, m. p. 206—210° (Found: C, 54·3; H, 5·2; N, 10·8. Calc. for $C_{54}H_{56}O_{21}N_{10}$: C, 54·8; H, 4·8; N, 11·8%).

Selenium dehydrogenation of vobtusine. Vobtusine (4 g.) and selenium (6 g.) were heated at 320—340° for 15 min. The cooled, powdered, product was exhaustively extracted with benzene, and the solution shaken with 2% acetic acid, 5% sulphuric acid, and 2N-ammonia, to give a slightly basic, basic, acid, and neutral (benzene residue) fractions. Both basic fractions were chromatographed in benzene over alumina to give a yellow oil. This oil gave a picrate which crystallised twice from methanol to give yellow needles, m. p. 200—202°, undepressed on admixture with quinoline picrate (Found: C, 50·0; H, 3·2. Calc. for $C_{18}H_{10}O_7N_4$: C, 50·3; H, 2·9%). The oil also gave a styphnate which crystallised twice from methanol to give needles, m. p. 207—209°, undepressed on admixture with quinoline styphnate (Found: C, 47·8; H, 2·7; N, 14·8. Calc. for $C_{18}H_{10}O_8N_4$: C, 48·1; H, 2·7; N, 15·0%).

Selenium dehydrogenation of voacangine. Voacangine and selenium were heated to 350° for 15 min. The ether extract of the ground mass gave an oil, b. p. 220°/700 mm., from which was obtained a picrate, m. p. 187—188° (Found: C, 48·1; H, 4·0. Calc. for $C_{14}H_{14}O_7N_4$: C, 48·0; H, 4·0%). 3-Ethyl-5-methylpyridine picrate has m. p. 187—188°.[5]

The authors acknowledge with thanks bursaries (to B. O. G. S. and A. A. V.), and grants from the S.A. Council for Scientific and Industrial Research.

DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF NATAL, PIETERMARITZBURG, SOUTH AFRICA. [*Received, June 23rd*, 1958.]

---

969. *The Reaction of Ethyl Diazoacetate with Thionaphthen.*

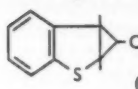
By G. M. BADGER, H. J. RODDA, and JENNETH M. SASSE.

THIONAPHTHEN and ethyl diazoacetate have been reported[1] to yield ethyl 2 : 3-dihydrothionaphthen-2 : 3-yleneacetate (I; R = Et). Further examination of the reaction leading to this ester has shown that at least three addition products are formed and that a compound previously isolated as its amide from the mixture of acids formed by hydrolysis and reductive desulphurisation of the adduct mixture, and thought to be 2-*cyclo*hexyl*cyclo*propanecarboxylic acid, is not this substance but is probably an ethyl*cyclo*heptanecarboxylic acid. 2-*cyclo*Hexyl*cyclo*propanecarboxylic acid should therefore be deleted from the literature.

Vacuum-distillation of the ester adduct from thionaphthen and ethyl diazoacetate gave two fractions, b. p. 86°/0·01 mm. and 98—110°/0·01 mm. respectively. The lower-boiling fraction, on alkaline hydrolysis, gave a mixture of acids from which the major constituent, 2 : 3-dihydrothionaphthen-2 : 3-yleneacetic acid-A (I; R = H; for designation see below), m. p. 148°, identical with that previously isolated,[1] was separated. Reductive desulphurisation of the mixed acids gave γ-phenylbutyric acid as the major product. The residues,

[1] Badger, Christie, Rodda, and Pryke, *J.*, 1958, 1179.

after separation of this acid, were treated with thionyl chloride and then aqueous ammonia, giving a small yield of an amide, m. p. 148°, identical with that product previously erroneously described as 2-*cyclo*hexyl*cyclo*propanecarboxyamide. In the earlier study [1] the total desulphurised acid was treated with thionyl chloride and aqueous ammonia; it has been shown that γ-phenylbutyric acid does not form an amide under these conditions, and the amide, m. p. 148°, was therefore the only acid derivative then isolated. This compound has now been found to be identical with the amide of an acid obtained by the hydrolysis and reduction of the adduct from ethyl diazoacetate and ethylbenzene; it is therefore probably an ethyl*cyclo*heptanecarboxyamide, the corresponding acid arising from the hydrolysis and reductive desulphurisation of a small amount of adduct formed by addition of ethyl diazoacetate to the benzo-ring of thionaphthen.



(I)

The higher-boiling fraction of the ester adduct (above) gave on hydrolysis 2 : 3-dihydrothionaphthen-2 : 3-yleneacetic acid-B (I; R = H), m. p. 182°. Reductive desulphurisation of this acid gave γ-phenylbutyric acid.

In keeping with the above results, freshly prepared W-7 Raney nickel reduced *trans*-2-phenyl*cyclo*propanecarboxylic acid to γ-phenylbutyric acid despite the previous failure [1] to achieve this reduction.

The 2 : 3-dihydrothionaphthen-2 : 3-yleneacetic acids-A and -B have very similar ultraviolet spectra, and as both gave γ-phenylbutyric acid on desulphurisation they must be stereoisomers. It has not been possible to assign unequivocally geometrical configurations to these acids, but it has been shown by paper chromatography that acid-B can be isomerised to acid-A *via* the acid chloride,[2] and that the reverse isomerisation does not occur. This indicates that acid-A is conformationally the more stable, a condition which would be fulfilled if this were the *trans*-acid with the smaller steric interaction between the ethoxycarbonyl group and the main bulk of the molecule.

Experimental.—2 : 3-*Dihydrothionaphthen*-2 : 3-*yleneacetic acid.* The crude adduct,[1] b. p. 126—160°/0·5 mm. (8·9 g.), was redistilled to give two fractions: (i) b. p. 86°/0·01 mm. (6·32 g.), and (ii) b. p. 98—110°/0·01 mm. (1·83 g.). Fraction (i) was chromatographed on alumina with light petroleum, then hydrolysed, and 2 : 3-dihydrothionaphthen-2 : 3-yleneacetic acid-A (1·3 g.) was isolated. It had m. p. 148°, unchanged on repeated recrystallisation; it showed only one spot on paper chromatography [3] (with butanol–ammonium carbonate buffer as solvent), R_F 0·55, and was identical with that previously isolated.[1] Fraction (ii) was similarly chromatographed and the material eluted with benzene, then hydrolysed, and the product recrystallised from light petroleum to give 2 : 3-*dihydrothionaphthen*-2 : 3-*yleneacetic acid-B* (0·35 g.), m. p. 182°, R_F 0·29 (Found: C, 62·4; H, 4·3; O, 16·4; S, 16·4. $C_{10}H_8O_2S$ requires C, 62·5; H, 4·3; O, 16·6; S, 16·7%). Its ultraviolet light absorption in 95% ethanol was very similar to that of the A-isomer and showed $\lambda_{max.}$ (log ε in parentheses) at 250 (3·92), 264 (3·73), and 292 mμ (3·16). Its 4-*phenylphenacyl ester* formed needles, m. p. 163° (Found: C, 74·4; H, 5·0; O, 12·8; S, 8·2. $C_{24}H_{18}O_3S$ requires C, 74·6; H, 4·7; O, 12·4; S, 8·3%).

Desulphurisations. The above A-acid (1·2 g.), in 1% aqueous sodium carbonate, was treated with W-7 Raney nickel (from 15 g. of alloy). The resulting oil showed only one spot on paper chromatography, but distillation gave fractions (i) b. p. 104°/0·01 mm. (0·3 g.) and (ii) b. p. 108—120°/0·01 mm. (0·61 g.). The latter solidified and gave γ-phenylbutyric acid (0·22 g.), m. p. 48—49°, identified by its infrared spectrum, its R_F (0·64), and by mixed m. p. The mother-liquors were added to fraction (i), which was treated with excess of thionyl chloride and then ammonia, to give an amide (20 mg.), m. p. 148°, not depressed on admixture with the amide previously obtained [1] (Found: C, 71·4, 71·3, 71·2; H, 11·2, 10·9, 10·8; N, 8·3. Calc. for ethyl*cyclo*heptanecarboxyamide, $C_{10}H_{19}ON$: C, 71·0; H, 11·3; N, 8·3%).

Desulphurisation of the B-acid (0·4 g.) gave an acid (0·32 g.; m. p. 37—40°) which showed only one spot on paper chromatography. Recrystallisation from water gave γ-phenylbutyric acid, m. p. and mixed m. p. 49°. Its identity was confirmed by paper chromatography (R_F 0·64) and by infrared spectroscopy.

[2] Cf. Burger and Yost, *J. Amer. Chem. Soc.*, 1948, **70**, 2198.
[3] Block, Durrum, and Zweig, "Paper Chromatography and Paper Electrophoresis," Academic Press, New York, 1955.

Reduction of trans-2-*phenyl*cyclo*propanecarboxylic acid with Raney nickel.* *trans*-2-Phenyl-*cyclo*propanecarboxylic acid (0·2 g.) was treated with freshly prepared W-7 Raney nickel (from 2·5 g. of alloy) in 1% aqueous sodium carbonate (25 c.c.) and stirred on the steam-bath for 1 hr. The resulting oil (0·2 g.) gave a solid (0·07 g.) which on recrystallisation from water formed plates, m. p. 48—49°, not depressed on admixture with authentic γ-phenylbutyric acid.

Reaction of ethyl diazoacetate with ethylbenzene. Ethyl diazoacetate (16 g.) in ethylbenzene (15 g.) was added dropwise, with stirring, to copper powder (0·5 g.) and ethylbenzene (30 g.) during 5 hr. at 145° (bath). More copper (0·5 g.) was added during the next 4 hr. Distillation gave ethylbenzene (34 g.) and fractions (i) b. p. 67—70°/0·4 mm. (1·5 g.), (ii) b. p. 74—78°/0·4 mm. (1·44 g.), and (iii) b. p. 140°/0·3 mm. (4 g.). Hydrolysis of fraction (i) gave fumaric acid. Hydrolysis of part of fraction (ii) (1 g.) gave a semisolid acid (0·5 g.). Washing with light petroleum (b. p. <40°) gave fumaric acid (0·02 g.), and the remaining oil (0·44 g.) was hydrogenated, in 1% aqueous sodium carbonate, over W-7 Raney nickel. Treatment of the resulting acid (0·4 g.) with thionyl chloride, and then ammonia, gave ethyl *cyclo*heptanecarboxyamide, identical (mixed m. p., infrared spectra) with the product described above.

UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA. [*Received, June 27th*, 1958.]

970. 1-*Ethyl*-3-*methyl*cyclo*pentadiene.*

By D. A. H. TAYLOR.

1-ETHYL-3-METHYL*cyclo*PENTADIENE has been prepared [1] by the decarboxylation of β-(2-carboxy-4-methyl*cyclo*pentadienyl)propionic acid, produced by self-condensation of lævulic acid. A specimen was required and was prepared by the action of ethylmagnesium bromide on 3-methyl*cyclo*pent-2-en-1-one. Although it reacted readily with the usual reagents for *cyclo*pentadiene, including maleic anhydride, crystalline products were not obtained, which suggests that it is a mixture of double-bond isomers.

The ultraviolet absorption maximum in hexane [$\lambda_{max.}$ 241 mμ (log ε 4·5)] agrees in position with the value $\lambda_{max.}$ 238 mμ (log ε 3·5) reported for *cyclo*pentadiene.[2] The larger extinction coefficient of our compound suggests that it may have an exocyclic double bond; thus the expected values [3] for 3-ethylidene-1-methyl*cyclo*pentene are $\lambda_{max.}$ 242 mμ (log $\varepsilon > 4$). In this case, isomerisation must precede reaction as a *cyclo*pentadiene.

Experimental.—1-*Ethyl*-3-*methyl*cyclo*pentadiene.* To the Grignard solution prepared from ethyl bromide (56 g.), magnesium (12 g.), and ether was added 3-methyl*cyclo*pent-2-en-1-one (48 g.).[4] The solution was decomposed with ammonium chloride solution, washed, and dried, and the ether evaporated. The residue was distilled, 1-ethyl-3-methyl*cyclo*pentadiene (15 g.) being collected as a liquid, b. p. 58°/50 mm., n_D^{20} 1·4688. No polymerisation occurred on redistillation at this pressure (Found: C, 88·7; H, 11·0. Calc. for C_8H_{12}: C, 88·9; H, 11·1%). The high-boiling residue was unchanged when heated.

UNIVERSITY COLLEGE, IBADAN, NIGERIA. [*Received, June 30th*, 1958.]

[1] Duden and Freydag, *Ber.*, 1903, **36**, 944.
[2] Scheibe, *Ber.*, 1926, **59**, 1333.
[3] Woodward, *J. Amer. Chem. Soc.*, 1942, **64**, 72; Fieser and Fieser, "Natural Products related to Phenanthrene," 3rd Edn., Reinhold, New York, 1949, p. 185.
[4] Acheson and Robinson, *J.*, 1952, 1127.

971. *Michael Addition of* 1-*Methyloxindole and Dimethyl Acetylenedicarboxylate.*

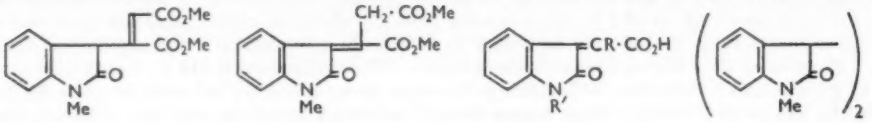
By J. A. BALLANTINE, R. J. S. BEER, and ALEXANDER ROBERTSON.

DURING an investigation of possible synthetical routes to γ-(5-hydroxy-3-indolyl)-α-3-oxindolyl-γ-oxobutyric acid, a degradation product of violacein,[1] attempts were made to effect a Michael reaction between 1-methyloxindole and dimethyl acetylenedicarboxylate in the presence of sodium methoxide. The two coloured compounds isolated gave almost identical analytical results, consistent with either of the expected products (I) or (II), and

[1] Ballantine, Barrett, Beer, Boggiano, Clarke, Eardley, Jennings, and Robertson, *J.*, 1957, 2222.

XUM

had ultraviolet absorption spectra very similar to those of α-3-oxindolylidenepropionic acid [2] (III; R = Me, R′ = H) and β-benzyl-α-(1-methyl-3-oxindolylidene)propionic acid [3]



(I) (II) (III) (IV)

(III; R = CH_2·COPh, R′ = Me). The coloured products are therefore regarded as different forms, possibly geometrical isomers, of dimethyl (1-methyl-3-oxindolylidene)succinate (II).

A third, colourless product is formulated as the bisoxindolyl (IV) in accordance with the analytical data and with its ultraviolet absorption spectrum ($\lambda_{max.}$ 253 mμ, log ε 4·13, in alcohol) which resembles that of 1-methyloxindole ($\lambda_{max.}$ 251 mμ, log ε 4·00). A compound with identical properties and infrared absorption spectrum was obtained by reduction of 1 : 1′-dimethyl*iso*indigotin [4] with zinc and acetic acid.

Ultraviolet absorption spectra.

Compound	$\lambda_{max.}$ (log ε)	$\lambda_{min.}$ (log ε)
Red product, m. p. 81°	261(4·40), 306(3·76)	232(3·83), 281(3·49)
Yellow product, m. p. 86°	263(4·42), 307(3·79)	234(3·85), 281(3·52)
(III; R = Me, R′ = H) [2]	262(4·38), 295(3·90)	230(3·85), 277(3·78)
(III; R = CH_2·CO·Ph, R′ = Me) [3]	258(4·37), 304(3·73)	224(4·08), 286(3·69)

Experimental.—Dimethyl (1-*methyl*-3-*oxindolylidene*)*succinate* (II). A solution of 1-methyloxindole (2·0 g.) in methanol (20 ml.) containing sodium methoxide (from 0·5 g. of sodium) was cooled to −5° and stirred (nitrogen atmosphere) whilst dimethyl acetylenedicarboxylate (2 ml.),[5] dissolved in a little methanol, was gradually added. The vessel was then sealed and kept at room temperature. After 30 days, the separated crystalline solid was removed and the filtrate poured into water, acidified, and extracted with ether. The gummy residue left after evaporation of the ether was extracted with light petroleum (b. p. 40—60°) and the combined extracts on concentration deposited a mixture (150 mg.) of the yellow and the red form of *dimethyl* (1-*methyl*-3-*oxindolylidene*)*succinate*, which were separated mechanically. The red form was freed from traces of the yellow form by digestion with a little warm light petroleum, and was thus obtained as dense prisms, m.p. 81° (Found: C, 62·1; H, 5·1; N, 4·7; OMe, 21·6. $C_{15}H_{15}O_5N$ requires C, 62·3; H, 5·2; N, 4·8; OMe, 21·5%) The yellow form separated from light petroleum in bright yellow needles, m.p. 86° (Found: C, 62·1; H, 5·1; N, 4·7; OMe, 21·4%) The red form was converted into the yellow by recrystallisation from light petroleum (b. p. 40—60°).

The solid which separated from the reaction mixture formed prisms (from methanol), m. p. 270° (decomp.) (Found: C, 74·0; H, 5·3; N, 9·4. $C_{18}H_{16}O_2N_2$ requires C, 73·8; H, 5·5; N, 9·6%). The same product, 1 : 1′-*dimethyl*-3 : 3′-*bisoxindolyl* (IV), m. p. and mixed. m. p. 270° (decomp. to a red liquid) (Found: C, 73·9; H, 5·5; N, 9·5%), was also obtained by reduction of 1 : 1′-dimethyl*iso*indigotin [4] with zinc dust in warm acetic acid.

UNIVERSITY OF LIVERPOOL. [*Received, July* 21*st*, 1958.]

[2] Julian, Printy, Ketcham, and Doone, *J. Amer. Chem. Soc.*, 1953, **75**, 5305.
[3] Barrett, Beer, Dodd, and Robertson, *J.*, 1957, 4810.
[4] Stollé, Bergdoll, Luther, Auerhahn, and Wacker, *J. prakt. Chem.*, 1930, **128**, 35.
[5] *Org. Synth.*, 1952, **32**, 55.

972. *Thallous* tert.-*Amyloxide.*

By D. C. BRADLEY.

RECENT studies [1] on the metal alkoxides have shown the striking effect of chain branching in the alkyl group on the degree of polymerisation of the metal alkoxide. Sidgwick and Sutton [2] showed that the lower monoalkoxides of thallium were tetrameric and assigned

[1] *E.g.*, Bradley, Mehrotra, and Wardlaw, *J.*, 1952, 2027; Bradley, Saad, and Wardlaw, *J.*, 1954, 3488.
[2] Sidgwick and Sutton, *J.*, 1930, 1461.

XUM

a structure to the tetramer. To gain information on the " chain-branching effect " in thallous alkoxides the *tert.*-amyloxide has been prepared. However, ebullioscopic measurements in benzene show that it is tetrameric over a twenty-fold change in concentration starting from a low concentration. This establishes that the tetramer involves a structure which can accommodate bulky alkyl groups without much intramolecular congestion

Experimental.—Thallous tert.*-amyloxide.* To thallous ethoxide (32·6 g., prepared by Menzies's method [3]) dissolved in benzene (80 c.c.), *tert.*-amyl alcohol (22·7 g.) was added and the benzene–ethyl alcohol azeotrope removed by fractional distillation. During evaporation of the solvent a mass of white crystals (33·5 g.) was deposited. From the mother liquor a second crop (4·7 g.) was obtained. Thallous *tert.*-amyloxide was dried at room temperature under reduced pressure and analysed by titrating samples in water with standard (*ca.* 0·1N) hydrochloric acid (Found: equiv. 292·9. Calc. for $TlOC_5H_{11}$: equiv. 291·53). The *tert.*-amyloxide decomposed above *ca.* 50° *in vacuo* and a solution in benzene deposited a mirror on the wall of the glass container on exposure to daylight.

Ebullioscopy. The previously described [4] all-glass ebulliometer with the differential water thermometer was used. The results are tabulated. The slope $\Delta T/m$ does not vary significantly

Wt. of solute m (g.)...	0·0611	0·1483	0·2541	0·3329	0·4466	0·6246	0·7588	0·8597	0·9670	1·2272
Elevation $\Delta T°$	0·0087	0·0213	0·0368	0·0484	0·0655	0·0916	0·1107	0·1257	0·1411	0·1797
$\Delta T/m$	0·1424	0·1436	0·1448	0·1454	0·1467	0·1466	0·1459	0·1462	0·1459	0·1464

with concentration and the average value (0·1454) gave $M = 1156$ (Calc. for $TlOC_5H_{11}$: 291·5). The weight of solvent was 17·53 g.

The author thanks Dr. R. C. Menzies for a loan of thallium and for his interest.

BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, July 29th*, 1958.]

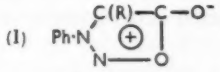
[3] Menzies, *J.*, 1931, 1571.
[4] Bradley, Gaze, and Wardlaw, *J.*, 1955, 3977.

---

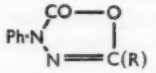
973. *Bromination of* N*-Phenylsydnone.*

By F. STANSFIELD.

THE formation of *C*-bromo-*N*-phenylsydnone (I; R = Br) by reaction of the *N*-phenylsydnone (I; R = H) with bromine has been described by Kenner and Mackay [1] who used glacial acetic acid as solvent, and also by Baker, Ollis, and Poole [2] who stated that use of acetic anhydride at 0° gave a smoother reaction and avoided the production of violet by-products.



(I)



(II)

On repeating the procedure of Baker *et al.*, I found that if the mixture of the sydnone, acetic anhydride, and bromine was warmed to 30—40°, a vigorous exothermic reaction took place with evolution of carbon dioxide. The product, formed in good yield, was 2-methyl-4-phenyl-1 : 3 : 4-oxadiazol-5-one (II; R = CH_3), and substitution of propionic or *n*-butyric anhydride for acetic anhydride gave the corresponding ethyl or *n*-propyl compound (II; R = C_2H_5 or *n*-C_3H_7), respectively.

That the reaction was catalysed by hydrogen bromide was shown by repeating the experiment in presence of anhydrous sodium acetate. Carbon dioxide was not evolved even when the temperature was raised to 95°, and 4-bromo-3-phenylsydnone was isolated. It is known that *N*-phenylsydnones in presence of mineral acid give phenylhydrazine derivatives [3] and such a compound may be an intermediate in the formation of the oxadiazolone.

[1] Kenner and Mackay, *Nature*, 1946, **158**, 910.
[2] Baker, Ollis, and Poole, *J.*, 1949, 313.
[3] Baker and Ollis, *Quart. Rev.*, 1957, **11**, 15.

XUM

A similar decomposition with evolution of carbon dioxide took place when a mixture of *N*-phenylsydnone, glacial acetic acid, and bromine was warmed gently, but no pure product was isolated.

Experimental.—*2-Methyl-4-phenyl-1 : 3 : 4-oxadiazol-5-one.* *N*-Phenylsydnone (3·0 g.) was suspended in acetic anhydride (15 ml.) at 0° and an ice-cold solution of bromine (1·5 ml.) in acetic anhydride (15 ml.) added with continued cooling. The sydnone dissolved and the *C*-bromo-compound soon began to separate. The mixture was placed in a water-bath which was gradually heated to boiling during 30 min. When the internal temperature reached 30—40° a vigorous reaction occurred with evolution of carbon dioxide, and finally the clear straw-coloured solution was poured into water (75 ml.). After shaking and heating to decompose excess of anhydride, the product was placed in the refrigerator overnight. The solid which separated was filtered off, washed with water, dried, and crystallised from light petroleum (b. p. 60—80°), giving slightly yellow needles (2·2 g., m. p. 89—90°). On recrystallisation from ethanol and from light petroleum, it formed colourless rhombs, m. p. 92·5—93° (Found: C, 61·6; H, 4·6; N, 15·7. Calc. for $C_9H_8O_2N_2$: C, 61·4; H, 4·5; N, 15·9%). These gave no depression of m. p. with authentic material prepared from 1-acetyl-2-phenylhydrazine and ethyl chloroformate.[4]

When the experiment was repeated in presence of anhydrous sodium acetate (7·5 g.), no carbon dioxide was evolved on heating the mixture in a boiling-water bath, and the product was 4-bromo-3-phenylsydnone (2·0 g., m. p. 135°, decomp.).

Using propionic anhydride we obtained 2-ethyl-4-phenyl-1 : 3 : 4-oxadiazol-5-one,[5] m. p. 60—61·5°.

n-Butyric anhydride gave the 2-n-*propyl compound* as slightly yellow needles from petroleum, m. p. 57·5—58·5° (Found: C, 64·7; H, 5·7; N, 14·1. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%).

The author thanks Dr. D. A. Peak for interest and encouragement.

UNIVERSITY OF KHARTOUM, SUDAN. [*Received, July 29th*, 1958.]

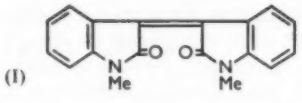
[4] Rupe and Gebhardt, *Ber.*, 1899, **32**, 10.
[5] Freund and Goldsmith, *Ber.*, 1888, **21**, 2461.

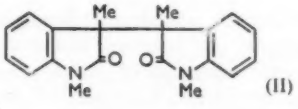
---

974. *Oxidative Dimerisation of Oxindoles.*

By JOHN HARLEY-MASON and R. F. J. INGLEBY.

OXIDATION of phenols by alkaline ferricyanide is well known [1] to produce a variety of coupling products *via* radical intermediates. Oxindoles exhibit pseudo-phenolic properties, and two similar oxidations in this field are now reported. Owing to the insolubility of the starting products in aqueous alkali, oxidation was conducted in a vigorously stirred two-phase system (water–carbon tetrachloride).





1-Methyloxindole gave in poor yield 1 : 1′-dimethyl*iso*indigo (I) while 1 : 3-dimethyloxindole gave in fair yield a mixture of the *meso*- and racemic forms of 1 : 3 : 1′ : 3′-tetramethyl-leuco*iso*indigo (II). The *meso*-configuration is tentatively assigned to the higher-melting and less-soluble isomer, though we have no direct evidence on this point. Examination of a model of (II) discloses very considerable crowding in the centre of the molecule, and it is noteworthy that attempts to obtain a similar structure by *C*-alkylation of 1 : 1′-dimethyl-leuco*iso*indigo were unsuccessful,[2] it being impossible to introduce more than one alkyl group because of steric hindrance.

[1] Thyagarajan, *Chem. Reviews*, 1958, **58**, 439.
[2] Faseeh and Harley-Mason, unpublished work.

Experimental.—1 : 1′-*Dimethylisoindigo* (I). A solution of 1-methyloxindole (1·0 g.) in carbon tetrachloride (30 c.c.) was heated at 80° under reflux and vigorously stirred while a solution of potassium ferricyanide (2·3 g.) and sodium hydroxide (0·4 g.) in water (30 c.c.) was added dropwise during 30 min. After cooling, the organic layer was separated, the aqueous layer was further extracted with carbon tetrachloride (20 c.c.), the combined extracts were dried ($MgSO_4$), and the solvent was removed. The residual red gum was taken up in ethanol; 1 : 1′-dimethyl*iso*indigo (0·1 g.) was slowly deposited at 0° as red needles, m. p. 268°; a mixture with an authentic sample [3] had m. p. 267—269°.

Oxidation of 1 : 3-*dimethyloxindole.* A solution of 1 : 3-dimethyloxindole (1·65 g.) in carbon tetrachloride (25 c.c.) was treated as above with potassium ferricyanide (3·5 g.) and sodium hydroxide (1·0 g.) in water (35 c.c.). The gum remaining after removal of carbon tetrachloride was taken up in ethanol, and an equal volume of ether added. Large prisms (0·2 g.), m. p. 219—221°, of meso-(?)-1 : 3 : 1′ : 3′-*tetramethyl-leucoisoindigo* (II) slowly separated at 0° (Found: C, 74·5; H, 6·1; N, 9·0. $C_{20}H_{20}O_2N_2$ requires C, 75·0; H, 6·3; N, 8·7%). The mother liquor was evaporated to dryness, and the residue, in benzene, chromatographed on acid-washed alumina. Needles (0·27 g.), m. p. 175°, of the racemic (?) *isomer* were obtained from the eluate (Found: C, 75·1; H, 6·3; N, 8·4%). Further elution with chloroform–ethanol gave a further 0·12 g. of the higher-melting isomer. The infrared spectra of the two isomers were extremely similar.

We thank the Department of Scientific and Industrial Research for a Maintenance Grant (to R. F. J. I.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 14th,* 1958.]

[3] Stollé, *J. prakt. Chem.*, 1930, **128**, 4.

975. *Thallous Borohydride*, $TlBH_4$.

By T. C. WADDINGTON.

THALLOUS borohydride, $TlBH_4$, has been prepared as a white crystalline solid, insoluble in water, but slowly decomposed on contact with water leaving a residue of metallic thallium. The crystal has the face-centred cubic NaCl structure with the unit-cell parameter $a = 6{\cdot}88_2$ Å and is isomorphous with the sodium, potassium, rubidium, and cæsium salts.[1,2] The insolubility in water indicates the similarity of the salt to thallous chloride, bromide, and iodide, but not to thallous fluoride, with which it is isoelectronic. The infrared spectrum of the salt in the region 4000—600 cm.$^{-1}$ has also been recorded, together with the infrared spectra of lithium, sodium, and potassium borohydrides (see Table). The borohydride ion has two infrared-active fundamental frequencies, ν_3 and ν_4; ν_3 is in the region of 2300 cm.$^{-1}$ whereas ν_4 is found at about 1100 cm.$^{-1}$. The spectra of lithium and sodium borohydrides have previously been reported by W. C. Price,[3] who, however, did not observe the splitting of the band in the region of 2300 cm.$^{-1}$. This splitting may perhaps be attributed to the failure of the BH_4^- ion to rotate freely in the crystal lattice, therefore removing the threefold degeneracy on the ν_3 vibration. The value of ν_3 for thallous borohydride is lowered by about 100 cm.$^{-1}$ relative to those of the alkali-metal borohydrides and the value of ν_4 is lowered by about 60 cm.$^{-1}$. This lowering perhaps indicates the beginning of multicentre bonding or a small covalent contribution to the bonding in the crystal lattice. This would also explain the insolubility of the salt in water.

Attempts to prepare silver borohydride failed, metallic silver always being produced, probably owing to the low electrode potential of the Ag^+ ion.

Infrared spectra (cm.$^{-1}$*) of the borohydrides (principal lines of the bands in italics).*

Salt	ν_3	ν_4	Salt	ν_3	ν_4
$LiBH_4$	2360, *2290*, 2210	1094	KBH_4	2370, *2280*, 2210	1117
$NaBH_4$	2390, *2290*, 2210	1120	$TlBH_4$	2240, *2180*, 2110	1050

[1] Abrahams and Kalnajs, *J. Chem. Phys.*, 1954, **22**, 434.
[2] Soldate, *J. Amer. Chem. Soc.*, 1947, **69**, 987.
[3] Price, *J. Chem. Phys.*, 1949, **17**, 1044.

XUM

Experimental.—Thallous borohydride was precipitated by mixing aqueous solutions of thallous nitrate and potassium borohydride, filtered quickly, and washed with alcohol and ether. After attempts to produce silver borohydride by mixing aqueous silver nitrate with potassium borohydride solutions had led to the precipitation of metallic silver, ethereal solutions of silver nitrate and lithium borohydride were employed. However, metallic silver was again precipitated.

The compounds were mulled with Nujol and with hexachlorobutadiene and their infrared spectra recorded on a Perkin-Elmer double-beam, recording, infrared spectrophotometer. The *X*-ray powder photograph was taken with Cu-K_α radiation, a sample being filled into a thin-walled Pyrex capillary and the capillary sealed off with picein wax. The value of a was computed from the mean value obtained from the ten highest lines on the *X*-ray powder photograph.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 19th*, 1958.]

---

976. *Hydrolysis of Ethyl 3-Oxo-octadecanoate.*

By D. W. S. EVANS.

THERE is an anomaly in the literature of ethyl 3-oxo-octadecanoate. According to Asahina and Nakayama [1] it can be converted into its acid by 2—4 hours' treatment at 100° with 2% alcoholic potassium hydroxide, no other decomposition taking place, but Helferich and Köster [2] had found ketonic fission by aqueous alkaline hydrolysis; this has now been found to be so for 2% alcoholic potassium hydroxide as well, almost pure heptadecan-2-one resulting.

The ethyl ester, obtained from 3-ethoxycarbonylnonadecane-2 : 4-dione, melted at 36·5°. Levene and Haller [3] gave 37—38°, but Asahina and Nakayama [1] reported that the compound which they obtained by a similar method melted at 104—105°. (For many higher 3-oxo-methyl esters, Ställberg-Stenhagen [4] found two crystal modifications, but these had only slightly different m. p.s.)

The m. p. of 3-oxo-octadecanoic acid, prepared from its methyl ester by cold acid hydrolysis, has been reported as 102—103,[5] 98—99,[6] and 99° (decomp.).[7] Evidently the compound of m. p. 64—65° obtained by Asahina and Nakayama was some other substance, and their starting material was not ethyl 3-oxo-octadecanoate.

Experimental.—Ethyl 3-oxo-octadecanoate, prepared by deacylation of 3-ethoxycarbonylnonadecane-2 : 4-dione, had m. p. 36·5° after four recrystallisations from 95% ethanol and one from light petroleum (b. p. 40—60°) (Found: C, 73·4; H, 11·6. Calc. for $C_{20}H_{38}O_3$: C, 73·6; H, 11·7%).

Hydrolysis. Under all conditions of alkaline hydrolysis tried, either ketonic cleavage occurred, or the 3-oxo-ester was unchanged. With the Japanese workers' method, white needles were obtained in almost 90% yield. After one crystallisation from benzene, and one from light petroleum (b. p. 40—60°), these melted sharply at 48° (heptadecan-2-one, m. p. 48°) (Found: C, 80·2; H, 13·3. Calc. for the ketone $C_{17}H_{34}O$: C, 80·2; H, 13·5. Calc. for the acid $C_{18}H_{34}O_3$: C, 72·4; H, 11·5%). The semicarbazone had m. p. 127·2 (Helferich and Köster [2] gave 127°).

I thank Dr. J. C. Roberts for his interest, and the Ministry of Education for a grant.

THE UNIVERSITY, NOTTINGHAM. [*Received, September 12th*, 1958.]

[1] Asahina and Nakayama, *J. Pharm. Soc. Japan*, 1925, **526**, 3.
[2] Helferich and Köster, *Ber.*, 1923, **56**, 2090; see also Breusch and Keskin, *Rev. Fac. Sci. Univ. Istanbul*, 1946, **11**, *A*, 24.
[3] Levene and Haller, *J. Biol. Chem.*, 1925, **63**, 671.
[4] Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1945, **20**, *A*, No. 19.
[5] Mitz, Axelrod, and Hofman, *J. Amer. Chem. Soc.*, 1950, **72**, 1231.
[6] Stenhagen, *Arkiv Kemi*, 1951, **3**, 381.
[7] Bergström, Aulin-Erdtman, Rolander, Stenhagen, and Östling, *Acta Chem. Scand.*, 1952, **6**, 1157.

XUM

XUM

XUM

THE CHEMICAL SOCIETY

PATRON

HER MAJESTY THE QUEEN

President

H. J. Emeléus, C.B.E., M.A., D.Sc., F.R.S.

Vice-Presidents

who have filled the office of President

Sir Ian Heilbron, D.S.O., D.Sc., LL.D., F.R.S.
Sir Cyril Hinshelwood, M.A., Sc.D., F.R.S.
E. L. Hirst, C.B.E., D.Sc., LL.D., F.R.S.
Sir Christopher Ingold, D.Sc., F.R.I.C., F.R.S.
Sir Eric Rideal, M.B.E., M.A., D.Sc., F.R.S.
W. Wardlaw, C.B.E., D.Sc., F.R.I.C.

Vice-Presidents

Wilson Baker, M.A., D.Sc., F.R.S.
R. P. Bell, M.A., F.R.S.
R. D. Haworth, D.Sc., Ph.D., F.R.S.
E. D. Hughes, D.Sc., F.R.I.C., F.R.S.
F. G. Mann, Sc.D., D.Sc., F.R.S.
L. E. Sutton, M.A., D.Phil., F.R.S.

Honorary Treasurer

M. W. Perrin, C.B.E., M.A., F.R.I.C.

Honorary Secretaries

J. Chatt, M.A., Sc.D., F.R.I.C.
M. J. S. Dewar, M.A., D.Phil.
A. W. Johnson, Sc.D., Ph.D., A.R.C.S.

Ordinary Members of Council

R. G. R. Bacon, Ph.D., A.R.C.S.
R. M. Barrer, D.Sc., Sc.D., F.R.S.
A. J. Birch, M.Sc., D.Phil., F.R.S.
R. C. Cookson, M.A., Ph.D.
A. G. Evans, Ph.D., D.Sc., F.R.I.C.
A. C. Farthing, M.A., B.Sc., A.R.I.C.
R. H. Hall, Ph.D., A.R.C.S., F.R.I.C.
B. A. Hems, D.Sc., F.R.I.C.
L. Hunter, Ph.D., D.Sc., F.R.I.C.
L. H. Long, Ph.D., A.R.C.S., D.I.C.
J. D. Loudon, Ph.D., D.Sc.
B. Lythgoe, Ph.D., F.R.I.C., F.R.S.
A. Maccoll, M.Sc., Ph.D.
R. S. Nyholm, D.Sc., F.R.I.C., F.R.S.
R. E. Richards, M.A., D.Phil.
L. A. K. Staveley, M.A.
J. C. Tatlow, Ph.D., D.Sc., F.R.I.C.
R. H. Thomson, D.Sc., Ph.D., F.R.I.C.
A. I. Vogel, D.Sc., D.I.C., F.R.I.C.
W. B. Whalley, D.Sc., Ph.D., F.R.I.C.
W. F. K. Wynne-Jones, D.Sc.

General Secretary

J. R. Ruck Keene, M.B.E., T.D., M.A.

Librarian

R. G. Griffin, F.L.A.

Deputy Librarian

J. Bird

XUM

Recent Aspects of the Inorganic Chemistry of Nitrogen

THIS report of a Symposium held at Cambridge in 1957 has been issued as No. 10 in the Society's series of ' Special Publications '.

The contributors include C. C. Addison and B. J. Hathaway (Nottingham), L. G. Bartha and Z. G. Szabo (Szeged), L. Batt with B. G. Gowenlock and J. Trotman (Birmingham), Professor Dr Margot Becke-Goehring (Heidelberg), C. A. Bunton with D. R. Llewellyn and G. Stedman (London), G. Hetherington and P. L. Robinson (Durham), W. C. E. Higginson (Manchester), J. Jander with E. Kurzbach and E. Schmid (Freiburg), J. Lewis and D. B. Sowerby (Sheffield), R. E. Richards (Oxford), F. Seel (Würzburg), D. A. Spratt (I.C.I., Billingham).

Price: £1 5*s.* 0*d.*

THE CHEMICAL SOCIETY
BURLINGTON HOUSE, LONDON, W.1

Printed in Great Britain by Richard Clay and Company, Ltd., Bungay, Suffolk.

XUM

XUM